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Archives of Internal Medicine

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THE BACTERIOLOGY OF THE BLOOD AND JOINTS IN CHRONIC INFECTIOUS ARTHRITIS *

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This study deals with the etiology of a form of chronic arthritis which has been variously referred to as rheumatoid arthritis, arthritis deformans or chronic infectious arthritis. Goldthwaite [1] and his school call it atrophic arthritis. It may be defined as a chronic inflammatory condition of the joints and periarticular tissues, characterized in the earlier stages by migratory swelling and stiffness of the joints, and in the later stages by more or less deformity and ankylosis. In the great majority of cases, several joints are involved; indeed, one of the most striking features of the disease is its tendency, if unchecked, to progress and finally to involve nearly every joint in the body.

The etiology of chronic deforming arthritis has long been a subject for debate. Perhaps no disease in the whole realm of internal medicine has been more prolific of hypotheses and theories. It has long been recognized that there were many predisposing factors, such as fatigue, cold and exposure, which played an important part in the actual onset of symptoms; but the exciting cause or agent has eluded the most persistent investigators.

The most important contribution to the etiology of chronic arthritis was that made by Billings [2] and his co-workers nearly twenty years ago, when they pointed out the relationship which existed between focal infection and chronic infectious arthritis. Other students of arthritis were quick to recognize the importance of this work, and now the rôle of focal infection in the etiology of this disease is widely recognized. Billings believed that the joint manifestations were nothing other than metastatic infections, and he preferred the term chronic infectious arthritis to arthritis deformans or rheumatoid arthritis.

* Submitted for publication, Feb. 15, 1929.

* From the Cornell Clinic and the Second (Cornell) Medical Division of Bellevue Hospital.

1. Goldthwaite, J. E.: Infectious Arthritis, Boston M. & S. J. **101**:363, 1904.

2. Billings, Frank: Chronic Focal Infections and Their Etiologic Relations to Arthritis and Nephritis, Arch. Int. Med. **9**:484 (April) 1912.

In spite of the popularity of the theory of focal infection, modern authorities are not entirely in agreement as to the importance of such foci in the etiology of chronic infectious arthritis. Furthermore, even among those who accept the theory of focal infection, there is considerable disagreement as to what bacteria are actually responsible for the disease. The almost constant presence of various forms of streptococci in the original foci of infection has naturally led to the presumption that some type of streptococcus was responsible for the arthritic condition as well as for the focal infection. Unfortunately, the bacterial flora in the tonsils and about the teeth is so varied and contains such a multiplicity of streptococcal types that it has been impossible to determine whether *Streptococcus viridans, Streptotoccus hemolyticus* or the indifferent streptococcus plays the etiologic part. This confusion is enhanced still further by the presence of just as many varieties of streptococci about the tonsils and teeth of healthy persons as in those patients suffering from chronic infectious arthritis.

McCrae [3] took the view that the condition is always secondary to a focal infection somewhere in the body, but doubted whether this means actual infection of the joint with organisms. He thought that the joint changes in many cases may be due to toxins. He ventured no opinion concerning the actual bacteria responsible for the disease.

Pemberton [4] expressed the belief that focal infection in the tonsils and teeth is responsible in many cases, but that a large variety of diseases of an infectious or inflammatory nature may act in an analogous way. He believed that the most important causative organisms are *Streptococcus hemolyticus* and *Streptococcus viridans*, "although probably any other organism is capable of producing the same results."

Osgood [5] stated that rheumatoid arthritis is a disease in which no specific organism has been found which can be held constantly responsible for its causation. He concluded that there are probably many different types of organisms and many other factors that play etiologic parts in its onset and course.

Nichols and Richardson,[6] after careful investigation of the pathologic changes in sixty-five cases of chronic arthritis, came to the conclusion that the lesions in the rheumatoid type might result from a great variety of origins, such as infection, disease and trauma.

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3. McCrae, T.: Arthritis Deformans in Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger, 1915, vol. 5, p. 895.

4. Pemberton, R.: Arthritis in Nelson's Loose-Leaf Living Medicine, vol. 5, p. 605.

5. Osgood, R. B.: The Orthopedic Aspects of Chronic Arthritis, J. Bone & J. Surg. **8**:1 (Jan.) 1926.

6. Nichols, F. H., and Richardson, F. L.: Arthritis Deformans, J. M. Research **16**:149, 1907.

Hench [7] of the Mayo Clinic expressed the belief that arthritis deformans is primarily of infectious origin. He emphasized the systemic nature of the condition.

A considerable amount of research has been carried out on the bacteriology of chronic infectious arthritis, but none of this can be said to have furnished conclusive information as to the exciting cause of the disease. The constant presence of various types of streptococci in the tonsils and about the teeth has naturally focused the interest of investigators on these organisms. Davis,[8] in 1911, took cultures from the various foci of infection which he found associated with chronic arthritis. In the great majority of cases, the hemolytic streptococcus was the predominating organism. With these streptococci, Davis was able to produce arthritis experimentally in rabbits. Blood cultures and cultures from the joint fluids of patients with chronic arthritis never gave positive results. However, Davis felt from his own investigations that the hemolytic streptococcus was probably the etiologic agent.

Working on the assumption that chronic deforming arthritis was a streptococcal disease, Hastings,[9] in 1913, resorted to the complement-fixation test as a method of determining which type of streptococcus was instrumental in causing the infection. By employing the old Wassermann technic, Hastings obtained positive complement fixation with the serum of arthritic patients and strains of streptococci isolated from foci of infection. In this way he believed that he could determine the exact biologic type of streptococcus with which the patient was infected.

More recently, Burbank and Hadjopoulos [10] have repeated Hastings' complement-fixation work with a slightly modified technic. They found that patients with periarticular or deforming arthritis reacted positively to some form of hemolytic streptococcus, whereas patients with osteoarthritis reacted positively to streptococci of the *viridans* groups.

E. C. Rosenow [11] was disposed to look on *Streptococcus viridans* as the exciting agent in chronic infectious arthritis. This investigator

7. Hench, P. S.: The Systematic Nature of Chronic Infectious Arthritis, Atlantic M. J. **28**:425 (April) 1925.

8. Davis, D. J.: Bacteriological and Experimental Observations on Focal Infections, Arch. Int. Med. **9**:505 (April) 1912; Chronic Streptococcus Arthritis, J. A. M. A. **61**:724 (Sept. 6) 1913.

9. Hastings, T. W.: Complement Fixation Tests for Streptococcus, Gonococcus and Other Bacteria in Infective Deforming Arthritis and Arthritis Deformans, J. A. M. A. **60**:1208 (April 13) 1913; Complement Fixation Tests in Chronic Infective Deforming Arthritis, J. Exper. Med. **20**:52, 1914.

10. Burbank, R., and Hadjopoulos, L. G.: Serologic Significance of Streptococci in Arthritis and Allied Conditions, J. A. M. A. **84**:637 (Feb. 28) 1925.

11. Rosenow, E. C.: The Etiology of Arthritis Deformans, J. A. M. A. **62**: 1146 (April 11) 1914.

took cultures from the enlarged lymph nodes of patients with chronic arthritis and was able to isolate *Streptococcus viridans* in a considerable number of cases.

Small [12] believed that a certain number of cases of chronic infectious arthritis are nothing more than a chronic form of rheumatic fever, and as such are referable to infection with the indifferent streptococcus (*Streptococcus cardio-arthritidis*).

From this review of the literature, it is evident that while bacteriologists have suspected the streptococcus as the exciting cause of chronic infectious arthritis, there is considerable disagreement among them as to which type or types of streptococcus are responsible for the disease.

The natural and obvious place to look for the causal agent of chronic infectious arthritis is in the joints involved. Unfortunately, efforts to cultivate bacteria from the joints themselves have not been consistently successful.

Rosenow,[11] in 1914, made cultures of the joint fluid in cases of chronic infectious arthritis and of the lymph nodes that drained the involved joints. He stated that in several instances he recovered *"Streptococcus viridans"* from both the glands and the joint fluid.

Moon and Edwards,[13] in 1917, took cultures from the joints in ten cases of chronic infectious arthritis, and recovered a "non-hemolytic streptococcus" in six cases. They did not give any further description of the streptococci found.

Richards,[14] in 1920, took cultures from the joints in fifty-four cases of chronic infectious arthritis, and isolated *"Streptococcus viridans"* in four cases.

Billings, Coleman and Hibbs,[15] in 1926, took cultures from the joints in fourteen cases of chronic infectious arthritis. One yielded a "hemolytic streptococcus"; five gave either a "non-hemolytic or a green producing streptococcus," and one gave a "mixed streptococcus culture with the non-hemolytic predominating." In six cases the results were negative, and in one the observations were not recorded.

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12. Small, J. C.: Rheumatic Fever: Observations Bearing on the Specificity of Streptococcus Cardioarthritidis in Rheumatic Fever and Sydenham's Chorea, Am. J. M. Sc. **175**:638 (May) 1928.

13. Moon, V. H., and Edwards, S. H.: Results of Blood Cultures in Rheumatoid Arthritis, J. Infect. Dis. **21**:154, 1917.

14. Richards, J. H.: Bacteriologic Studies in Chronic Arthritis and Chorea, J. Bacteriol. **5**:511, 1920.

15. Billings, F.; Coleman, G. H., and Hibbs, W. G.: Chronic Infectious Arthritis: Statistical Report with End-Results, J. A. M. A. **78**:1097 (April 15) 1922.

H. Warren Crowe [16] took cultures from the joint tissue of five patients suffering from rheumatoid arthritis, and isolated a staphylococcus, *Micrococcus deformans,* in four of five instances. Control cultures from tissue removed from nonarthritic patients did not show this organism.

Forkner, Shands and Poston [17] recently took cultures from the joints in sixty-three cases of chronic infectious arthritis, recovering organisms in fourteen, or 22 per cent. Eleven of the joint cultures contained *"Streptococcus viridans,"* two yielded gonococcus, and one, *Staphylococcus aureus.* Cultures of the lymph nodes draining the involved joints were made in twenty-one cases. Ten of these cultures were positive, nine showing *Streptococcus viridans* and one, gonococcus.

During recent years, several investigators have studied the bacteriology of the blood in rheumatoid arthritis.

Moon and Edwards,[13] in 1917, using Rosenow's technic, made blood cultures in eighty-three cases of rheumatoid arthritis, and recovered a "non-hemolytic streptococcus" in eighteen. They felt, however, that a diphtheroid bacillus, or *B. mucosus-capsulatus,* as well as the streptococcus, could act as the exciting agent in this disease. Moon and Edwards made no attempt to classify the streptococci which they isolated by sugars or immunologic tests. Furthermore, they did not report on nonrheumatoid conditions.

Richards,[14] in 1920, made blood cultures in cases of chronic arthritis, making use of North's medium. Blood cultures were taken in 104 cases of chronic infectious arthritis, and fourteen yielded positive results. Richards referred to the organism as *"Streptococcus viridans,"* although he remarked that the character of the growth was not always typical, only three of his strains showing green in the original culture.

Hadjopoulos and Burbank [18] took cultures from the blood in 145 cases of chronic arthritis and obtained a streptococcus in fifteen (10 per cent). Nine of these strains produced hemolysis, while six were of the viridans type. In eight cases a diphtheroid bacillus was obtained, while five others showed *Staphylococcus aureus.* Hadjopoulos and Burbank do not give the technic employed other than to state that their success was due to "neutralization of alexin in the freshly drawn blood." No control cultures were reported. These investigators were able to produce an experimental arthritis in rabbits with their streptococci.

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16. Crowe, H. Warren: Bacteriology and Surgery of Chronic Infectious Arthritis, New York, Oxford University Press, 1927.

17. Forkner, C. E.; Shands, A. R., and Poston, M. A.: Synovial Fluid in Chronic Arthritis, Arch. Int. Med. **42**:675 (Nov.) 1928.

18. Hadjopoulos, L. G., and Burbank, R.: A Preliminary Study Bearing on the Specific Causative Factors of Multiple Infective Arthritis, J. Bone & Joint Surg. **9**:278 (April) 1927.

Syranyi and Forro [19] recently took cultures from the blood in twenty-five cases of "polyarthritis" and obtained a streptococcus in 68 per cent. In nineteen of the cases described as "polyarthritis with fever," fourteen, or 73.6 per cent, were positive. In the remaining six cases in the group, referred to as "polyarthritis without fever," three, or 50 per cent, were positive. The organism isolated by Syranyi and Forro was classified as *Streptococcus viridans.* The various strains differed slightly in their reactions on the sugars, but they all fermented saccharose, salicin and lactose. These investigators did not report any experimental work on animals.

H. Warren Crowe [16] took cultures from the urine of patients suffering from rheumatoid arthritis and isolated a staphylococcus, *Micrococcus deformans,* in a high percentage of cases. *Micrococcus deformans* was not found in control cultures. He was unable to produce an experimental arthritis in animals with these staphylococci.

From this brief review of the literature, several conclusions seem justified:

1. While the relation of focal infection to chronic infectious arthritis is rather generally recognized, there is doubt in the minds of many as to whether the joint manifestations are actually metastatic infections or whether they are merely an expression of some toxic influence on the joint.

2. In respect to the bacterial agent responsible for the disease, a majority of the investigators look on the streptococcus as the exciting cause, but some believe that the staphylococcus, the gonococcus, the diphtheroid bacillus or some other micro-organism, as well as the streptococcus, can produce a deforming arthritis.

3. Even among those investigators who accept the streptococcus as a cause of rheumatoid arthritis, there is considerable disagreement as to which type of streptococcus is responsible, some considering it a *Streptococcus hemolyticus* infection, while others look on the indifferent or the green streptococcus as the causative agent. Another group of writers believes that deforming arthritis can be caused by any of the various types of streptococci.

4. A number of workers have found streptococci in the joints and even in the blood stream in cases of chronic infectious arthritis, but the results have been inconsistent and uncontrolled.

5. There has been little effort made to study the biologic relations between the streptococci which have been isolated from the blood and joints of arthritic patients.

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19. Syranyi, L., and Forro, E.: Streptokken im Blute mit besonderer Berücksichtigung der rheumatischen gelenkent Zungung, Klin. Wchnschr. **7**:453, 1928.

THE PRESENT STUDY

Two years ago the present study was initiated in the Cornell Clinic by taking cultures from the tonsils and teeth of patients afflicted with chronic infectious arthritis. Later on the scope of the study was extended, and cultures were also taken from the blood and, when possible, from the joints. It is principally with the blood and joint cultures that the present report is concerned.

The type of patient in whom we have been particularly interested presents a rather characteristic clinical syndrome, namely, a chronic polyarthritis with swelling and often with some deformity and ankylosis of the joints affected. In order to delineate still more clearly the type of case studied, we submit the following composite picture:

The patient, usually of the neurotic type, gives a history of sudden or gradual development of pain, stiffness and swelling in several joints. He often dates the onset of his symptoms to some disturbance in his physical equilibrium, such as a trauma, an acute infection, exposure to cold or a surgical operation. Occasionally the onset of symptoms dates back to an attack of rheumatic fever. When the onset is sudden, the patient may run an irregular fever varying from 99 to 101 F.; but when the onset is insidious, the temperature usually remains normal. The disease is almost always migratory in its early stages, jumping from joint to joint much as in rheumatic fever. After several attacks, however, the joints chiefly affected become permanently injured, and the process assumes a persistently chronic course.

The infection is prone to make its first appearance in the interphalangeal joints of the hands, frequently involving also the metacarpophalangeal joints of the fore and middle fingers. The joints gradually swell, with little or no pain, and in the course of time cause the fingers to assume the characteristic fusiform appearance. The knees are involved almost as frequently as the fingers. As the disease advances and involves other joints, the patient becomes uncomfortable. There is considerable disability, due to pain and stiffness on motion, and often there is persistent pain at night which interferes with the patient's sleep. The muscles become weak from disuse, and undergo atrophy. As a result, the patient's capacity for work and exercise is greatly diminished. Unless the disease is checked in its course, partial or complete ankylosis may occur in one or more joints.

On physical examination, the patient with chronic infectious arthritis presents a fairly typical picture. He is usually anemic, with a hemoglobin of seventy or under. If the condition is of long standing, the patient often appears chronically ill and undernourished; on the other hand, if it is an early case, the patient may be well nourished. The hands are cold and clammy and covered with perspiration. The swollen finger joints, which are characteristic, have on palpation a peculiar doughy or

rubber-like consistency, and in some instances the skin overlying the joint may become slightly bluish. The enlargement of the joint is due to the swelling and thickening of the synovial membrane and capsular ligaments. There is little if any pain on pressure, and only moderate pain on movement of the joint. In the larger joints, the signs of inflammation are more marked. There is more tenderness on pressure and more pain with movement. There may be an effusion of fluid in some of the larger joints. Of all the large joints, the knees are the most frequently affected. In a well established infection, the ankles, wrists, elbows and shoulders are usually implicated. The hip joints usually escape until late in the disease. The intervertebral joints are frequently involved, particularly in the cervical and lumbar regions. The temporomaxillary joints are frequently affected.

In the late stages of the disease, that is, after several years duration, more or less deformity and ankylosis develop, particularly in the hands and feet. Ulnar deviation of the fingers is a common occurrence.

Infectious arthritis runs a chronic course, extending over years. Usually, however, the progress is not continuous, periods of comparative comfort alternating with periods of active advance. With each attack there is a tendency for the joints to become progressively stiffer and more permanently injured.

Unless the disease is checked, the final stage is that of arthritis deformans. In the later stages, some of the periarticular swelling may disappear, due to the contraction of the fibrous tissue. In the joint itself, the granulation tissue becomes converted into adhesions which lead to immobilization. Late in the disease, bony changes also make their appearance. With loss of function, muscular atrophy becomes more and more pronounced. Many of these patients present a pitiful picture wtih their contracted, deformed limbs and marked wasting of the muscular tissue. Cardiac involvement is rare, even in advanced cases.

METHODS

1. *Blood Cultures.*—The technic employed for blood cultures was an adaptation of that recommended by Clawson[20] in his blood culture studies of rheumatic fever.

Twenty cubic centimeters of blood was taken aseptically from the arm with a Luer syringe, placed in two sterile culture tubes and allowed to clot. Each tube was treated separately in the following way:

The tube was centrifugated, and all the serum drawn off with a sterile pipet. The clot was then broken up in the original culture tube with a sterile glass tube, ¼ inch (6.35 mm.) in diameter. The fragments of clot were drawn up in the same glass tube, and transferred to a 3 ounce bottle containing 50 cc. of beef heart infusion broth with a p_H of 7.6 (0.5 per cent sodium chloride, 1 per cent peptone). The bottle was then put in the incubator at 37 C. and left there unopened for five days.

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20. Clawson, B. J.: Studies on the Etiology of Acute Rheumatic Fever, J. Infect. Dis. **36**:444 (May) 1925.

At the end of this time, a tube containing 8 cc. of a 1.5 per cent beef heart infusion agar was placed in the water bath and heated until the agar was completely melted. The tube was then partially cooled and 0.5 cc. of whole rabbit blood added to it. Finally, the tube was seeded with 0.1 cc. of broth from the original blood culture, and the contents poured into a petri dish. The culture was allowed to incubate for from twenty-four to forty-eight hours. Similar pour-plate cultures were made every three to five days thereafter until the original blood culture had been in incubation for thirty days. If, at the end of this time, the subcultures were still sterile, the sediment in the original blood culture bottle was drawn out with a sterile glass tube and centrifugated. After centrifugating, part of the sediment was examined by means of stained smears, while the remainder was cultured, part of it in fresh blood broth and part of it on blood agar plates. If these final cultures from the sediment showed no growth, the blood culture was considered sterile.

All of these cultures and transfers were made under a hood, in order to eliminate contaminations as far as possible. All contaminated cultures were discarded.

When colonies appeared on the plates, they were transferred into blood broth and identified by the usual bacteriologic methods.

2. *Joint Cultures.*—Cultures from joints were made in blood broth from synovial fluid or synovial membrane, or from bony curettings removed from the joint at operation. When only tissue was available, the material was put in a bottle containing blood broth and macerated with a glass rod. These cultures, like the blood cultures, were incubated for several weeks and subcultured from time to time.

BLOOD CULTURES

One or more blood cultures were made from seventy-eight patients with chronic infectious arthritis (table 1). For the most part, the patients in this series presented the clinical picture already described, namely, pain and stiffness and usually swelling in several joints. In rare instances, only one joint was affected at the time the patient came under observation, but a careful history brought out the fact that other joints had previously been involved. In addition to pain, stiffness and swelling of the joints, most of the patients presented some deformity and ankylosis of the joints affected. Thirty-six of the seventy-eight patients showed one or more characteristic fusiform fingers. The ages of the patients varied from 7 to 74 years. Fifty-nine were under 50 years of age, while eighteen were 50 or over. The age of one patient was not obtained. The duration of the disease varied from one month to thirty-five years, but in a majority of the cases the disease had existed from one to three years at the time the patient came under observation. With a few exceptions, the patients were free from fever at the time cultures were taken.

In this group of seventy-eight patients, the blood cultures of forty-eight, or 61.5 per cent, were found, after varying periods of incubation, to contain a gram-positive micrococcus, growing either in pairs or in short chains. This micro-organism presented all the morphologic characteristics of a streptococcus (table 2). Some of the patients whose

TABLE 1.—*A Resumé of Cases Studied with Results of Blood and Joint Cultures*

History Number	Age	Sex	Duration of Arthritis	Probable Focus of Infection	Joints Affected*	Blood Cultures†				Streptococcus Recovered Blood‡	Strain Number	General Remarks
						1	2	3	4			
C-100	38	M	2 yr.	?	F,V,K,A	—	+	..	..	T.S.	B-1	Synovial membrane from fusiform
C-101	28	F	2 yr.	Tonsils	F,W,A,T	+	+	(—)	..	T.S.	B-2	finger yielded no organism
C-102	63	F	14 yr.	Sinus	F,E,K	+	..	..	..	T.S.	B-3	
C-103	38	F	10 yr.	?	F,W,A	+	..	..	..	T.S.	B-4	
C-104	38	F	2 yr.	?	F,S	+	+	..	..	T.S.	B-5	
C-105	54	F	3 yr.	?	F,A	+	+	(—)	..	T.S.	B-6	
C-106	40	F	4 yr.	Tonsils	F,K,A	—	+	..	..	T.S.	B-7	
C-107	..	F	4 yr.	?	F,W	+	+	..	..	T.S.	B-8	Synovial membrane from fusiform
C-108	60	F	3 yr.	?	F,W,V	+	(—)	..	..	T.S.	B-9	finger yielded no organism
A-35972	33	F	1 yr.	Colon	F,T	+	D	(—)	..	T.S.	B-10	
A-5237	26	F	5 yr.	Tonsils	F,K,S,A	+	..	..	..	T.S.	B-11	
A-18049	58	F	1 yr.	Tonsils	F,H	+	+	..	..	T.S.	B-12	
A-97225	35	F	5 yr.	Tonsils	F,K	+	(—)	..	..	T.S.	B-13	
A-70282	39	F	4 yr.	Tonsils	F,A,K	+	..	..	..	T.S.	B-14	
A-9529	7	F	8 mo.	?	F,W,K	+	(—)	..	..	T.S.	B-15	
A-67550	11	F	4 yr.	?	F	+	(—)	..	..	T.S.	B-16	
A-17477	57	M	5 yr.	?	F,S	+	..	..	..	T.S.	B-17	Psoriasis
A-15541	58	F	4 yr.	Tonsils	F,W,K	+	+	(—)	..	T.S.	B-18	
A-10247	38	F	2 yr.	Colon	F,H	+	..	..	..	T.S.	B-19	
A-10410	62	F	5 yr.	?	F,W	+	..	..	..	T.S.	B-20	
A-20132	27	F	1 yr.	Tonsils	F,E,W,K	+	..	..	..	T.S.	B-21	
A-17688	50	F	2 yr.	Tonsils	F,E,K	+	(—)	..	..	T.S.	B-22	
C-109	55	F	6 wk.	Teeth	A,T	+	..	..	..	T.S.	B-29	Erythema nodosum
A-13920	52	F	2 yr.	Tonsils	F,W	+	(—)	..	..	T.S.	B-23	
R-100	28	M	9 mo.	Tonsils	F,S,K,A	+	..	..	..	T.S.	B-24	
A-14753	53	M	2 yr.	Tonsils	F,A,K	—	+	..	..	T.S.	B-25	
N-100	74	F	15 yr.	Tonsils	F,E,S	+	—	..	..	T.S.	B-26	
A-7466	26	F	5 yr.	?	K,S	+	Z	+	..	T.S.	B-27	
A-94403	23	F	1 mo.	Tonsils	K,F	+	..	..	..	T.S.	B-28	Erythema bullosum; same organism
R-103	44	F	2 yr.	Tonsils	F,S,H	+	..	..	..	T.S.	B-32	recovered from bullae
H-100	28	F	6 mo.	?	F,A,K	+	..	..	..	T.S.	B-48	
R-101	61	M	10 yr.	Teeth	H,W	+	..	..	..	T.S.	B-30	Curettings from hip joint and pus from
A-11301	49	M	2 yr.	Tonsils	F,K,V	+	+	(+)	(—)	T.S.	B-40	tooth yielded same organism
A-13013	26	F	6 wk.	Tonsils	J	+	(—)	..	..	T.S.	B-41	Erythema nodosum
A-48061	53	M	5 yr.	Tonsils	H,V	+	(—)	..	..	T.S.	B-42	
A-19568	30	F	2 yr.	Tonsils	K	+	..	.	..	T.S.	B-43	Psoriasis
A-97227	51	F	5 mo.	Intest.	F,W,K	—	+	..	..	T.S.	B-44	
C-118	14	F	4 mo.	?	F,A,H	+	..	..	..	T.S.	B-46	
R-106	35	M	?	?	F,K,S,F	+	..	..	..	T.S.	B-52	
A-92014	39	F	2 yr.	Tonsils	F,K,A	+	..	..	..	T.S.	B-51	

C-110	56	F	35 yr.	?	F,A,T	+	+	..	..	S.V.	B-33	
C-111	31	F	3 yr.	Tonsils	F,A,K	—	—	+	..	S.V.	B-34	
A-23020	28	F	1 yr.	?	A,K	—	+	..	..	S.V.	B-36	
D-100	14	F	3 yr.	?	H	+	..	..	..	S.V.	B-47	Curettings from head of femur yielded same organism
C-121	40	F	?	?	F,K	+	..	..	..	S.V.	B-49	
A-1955	41	F	3 yr.	?	H	+	(—)	..	..	S.V.	B-45	
A-19244	25	F	6 mo.	Sinus	W,K	+	..	..	..	S.N-H	B-35	
R-105	35	F	9 yr.	?	F,J,S,V	+	..	..	..	S.N-H	B-50	
N-101	32	F	4 yr.	Tonsils	F,W,A,K	Z	(—)	..	..	....	B-31	
A-1936	32	M	?	?	K	D	D	..	..	....	B-39	Synovial membrane of right knee yielded a pure culture of S.N-H
A-18127	27	F	5 yr.	Tonsils	K,E	D	D	..	..	....	B-37	Same organism recovered from knee fluid
A-19685	28	M	5 yr.	?	A,K	D	D	..	..	....	B-38	
C-112	54	F	6 mo.	?	F,K	—	..	..	..	....	....	
A-75724	23	M	7 mo.	?	H,W,F	—	..	..	..	....	....	
C-114	19	F	1 yr.	?	F,T,A	—	..	..	.	....	....	
C-115	42	F	2 yr.	?	F,S,K	—	—	—	—	....	....	
C-116	47	F	7 yr.	Tonsils	F,W,K	—	..	..	.	....	....	
A-23317	38	F	3 yr.	?	F,K,S,T	—	..	..	..	....	....	
A-25943	48	F	2 yr.	Tonsils	F,W	—	..	..	..	....	....	
A-22116	26	F	2 yr.	Tonsils	F,K,S	—	..	..	..	....	....	
A-14605	02	F	6 yr.	Tonsils	F,K	—	..	..	..	....	....	
A-13811	34	F	1 yr.	Tonsils	F,E,A	—	—	—	..	....	....	
A-14200	12	F	2 yr.	Teeth	F,K,A	—	—	..	.	....	....	
A-19931	47	F	2 yr.	Tonsils	F	—	..	..	..	....	....	
A-6729	35	F	10 yr.	Tonsils	F,W,A	—	—	..	..	....	....	
A-93793	45	F	6 mo.	Tonsils	F,K,A	—	—	..	..	....	....	
A-22985	28	F	8 mo.	?	F,E	—	..	..	..	....	....	
A-82050	32	F	4 yr.	?	F,T,W	—	—	..	..	....	....	
A-1172	38	M	3 yr.	Tonsils	A,W	—	..	..	.	....	....	
C-117	24	F	5 mo.	?	K,A	—	..	..	..	....	....	
R-104	40	M	9 mo.	?	F,S,J,K	—	..	..	..	....	....	
C-119	68	F	3 yr.	?	F	—	..	..	..	....	....	
A-30088	49	F	2 yr.	?	S,H	—	..	..	..	....	....	
A-24774	25	M	2 yr.	?	V	—	..	..	..	....	....	Infectious spondylitis
A-16716	48	F	2 yr.	?	W,A	—	—	..	..	....	....	
A-15561	41	F	2 yr.	Tonsils	W,S	—	—	..	..	....	....	
C-120	47	M	15 yr.	?	F,S	—	..	..	..	....	....	
C-122	37	F	8 yr.	Tonsils	K,H	—	—	..	..	....	....	T.S. recovered from knee fluid

* A indicates ankle; E, elbow; F, fingers; H, hip; J, jaw; K, knee; S, shoulder; T, toes; V, vertebrae; W, wrist.

† + indicates positive for streptococcus; D, Diphtheroid bacillus; Z, Micrococcus zymogenes; —, no growth; ( ) is used to indicate that patient had received vaccine treatment.

‡ T.S. indicates "typical strain"; S.V., Streptococcus viridans; S.N-H, Streptococcus nonhemolyticus.

blood cultures yielded this organism on the first culture showed the same organism in the blood on the second or even third culture. In other patients one blood culture was positive while the second was sterile or vice versa, indicating that the micro-organism was not constantly present in the blood stream. Most of the cases were ambulatory. Comparatively few patients were confined to their beds. The impression prevailed that streptococci were more likely to appear in the blood stream during an exacerbation of joint symptoms.

The number of cases studied was too small to make any definite statement regarding the relationship between *Streptococcus bacteremia* and the duration of the disease, but there appeared to be a higher percentage of positive blood cultures in patients over 50 and in those who had had the disease for a number of years. One patient (A-94403) with a positive blood culture had had joint symptoms for only one

TABLE 2.—*Summary of Bacteriologic Observations in Blood Cultures of Patients with Chronic Infectious Arthritis*

Type of Organism Found	Number of Cases
Typical strain (T.S.)	40
Streptococcus viridans (S.V.)	6 } 48
Streptococcus nonhemolyticus (S.N-H.)	2
Diphtheroid bacillus (D)	4
Micrococcus zymogenes (Z)	2

month. On the other hand, another patient (C-110) had been a sufferer from arthritis for thirty-five years. The following protocol is a good illustration of the type of patient on whom blood cultures have yielded streptococci.

A man (C-100), aged 38, came under observation on Jan. 18, 1928. Following an attack of influenza two years previously, he began to have pain and stiffness in the fingers and shoulders. Within six months the pain had spread to practically every joint in the body and his ankles, knees and fingers had become swollen. When first seen, the chief symptoms were in the hands and feet, although occasional flare-ups occurred in other joints. The tonsils had been removed two years before, and several abscessed teeth had been extracted.

On physical examination, the patient was found to have several fusiform fingers on each hand (fig. 1), a stiff neck, swollen ankles and feet and crepitation in the knees. Otherwise, the results of the physical examination were negative.

On January 19, a blood culture was taken. There was no growth after twenty-eight days of incubation.

On February 2, a second blood culture was taken. A streptococcus was recovered on the seventeenth day of incubation.

Clinically, this patient presented the typical picture of chronic infectious arthritis. The second blood culture yielded a streptococcus which on culture mediums resembled in some respects *Streptococcus viridans* and in others, *Streptococcus hemolyticus.*

Other Bacteria Isolated From Blood Cultures.—Although some type of streptococcus has been by far the most frequent observation in our blood culture studies, other bacteria have occasionally been isolated. A diphtheroid bacillus was recovered from the blood cultures in four cases. In one of these (A-19685), a diphtheroid bacillus was isolated twice from the blood, and cultures from the cloudy fluid obtained from the knee joint yielded the same organism in pure culture. In another case (A-35972), the first blood culture showed a streptococcus, while the second revealed a diphtheroid bacillus in pure culture.

Fig. 1.—Typical fusiform fingers in patient C-100 with chronic infectious arthritis. A "typical strain" of streptococcus was isolated from the patient's blood.

In two cases of chronic infectious arthritis, *Micrococcus zymogenes* was recovered from the blood. In one of these (A-7466), the first blood culture showed a streptococcus, the second culture *Micrococcus zymogenes*, while the third culture yielded a streptococcus similar in all respects to the streptococcus first isolated.

Staphylococcus albus was occasionally isolated from the blood cultures, but in view of the frequent occurrence of this organism as a con-

taminant in blood cultures, we have not been disposed to attach any significance to its presence.

Control Cultures.—It seemed important to check these observations in the blood of patients with chronic infectious arthritis by a series of blood cultures on patients with various other types of arthritis, on patients suffering from other infectious diseases, and on normal persons. Altogether, fifty-four controls were studied by means of blood cultures, the technic being similar in all respects to that used on patients with chronic infectious arthritis (table 3).

All the controls yielded sterile blood cultures. It is particularly interesting to note that seventeen cases of degenerative arthritis showed negative results. Four cases of gonococcal arthritis, three of chronic myositis and one of Still's disease showed no bacteremia.

TABLE 3.—*Classification of Patients Studied by Blood Culture*

	Number of Cases Cultured	Total	Streptococcus in Blood Culture
Chronic infectious arthritis	78	78	48
Controls			
Degenerative arthritis	17	54	0
Gonococcal arthritis	4		
Rheumatic carditis	6		
Still's disease	1		
Chronic myositis	3		
Chronic neuritis	3		
Gout	1		
Chorea	2		
Tuberculous adenitis	2		
Diabetic neuritis	1		
Convalescent pneumonia	7		
Iridocyclitis	1		
Weak foot	1		
Normal persons	5		

JOINT CULTURES

In seven cases of chronic infectious arthritis, the opportunity presented itself for taking intra-vitam cultures directly from one of the involved joints (table 4). In six of the seven cases, synovial membrane or bony curettings were available, while in the seventh case cultures were taken from the synovial fluid of the knee joint. With two exceptions, all the cases fell definitely into the group of chronic infectious arthritis.

One exceptional case, D-100, was that of a child, 11 years of age, who developed a septic arthritis of the left hip during an attack of pneumonia. The hip joint was opened and drained. After the wound had healed the patient continued to have pain and stiffness in the hip. After three years of discomfort and partial ankylosis, a reconstruction operation was performed on the left hip joint, and at this time cultures were taken from small bits of bony curettings. *Streptococcus viridans* was recovered from the joint tissue, similar in all respects to that recovered from the blood.

The other exceptional case in this series, A-1936, was that of a man, 32 years of age, who had his knee injured in an automobile accident. Shortly afterward, stiffness and pain developed in the knee which had been subjected to trauma. No other joints ever became involved. Physical examination showed a swollen fluctuating knee with considerable atrophy of the muscles above and below the joint. An arthroplastic operation was performed; a piece of synovial membrane was removed, and cultures were made. A nonhemolytic streptococcus was isolated from the culture. It is interesting to note that two blood cultures from this patient yielded in each case a pure culture of a diphtheroid bacillus.

In C-100 and C-107, both typical cases of chronic infectious arthritis with swollen joints and fusiform fingers, synovial membrane was removed from one of the fusiform finger joints and cultures were made. In both instances the cultures were negative for streptococci, though both patients had shown streptococci in blood cultures. Perhaps the fact that the material in these two cases was rather scanty was responsible for the negative results obtained.

A woman (C-121), aged 37, had had pain and swelling of both knees for eight years. She also had pain in the left hip and lumbosacral region of four years'

TABLE 4.—*Results of Cultures from Joints of Patients with Chronic Arthritis* *

No. of Cases	Material Cultured	Organism Recovered from Joint	Organism Recovered from Blood
R-101	Curettings from hip joint.....	Streptococcus (T.S.)	Streptococcus (T.S.)
D-100	Curettings from hip joint.....	Streptococcus viridans	Streptococcus viridans
A-1936	Synovial membrane from knee joint	Streptococcus (S.N-H.)	Diphtheroid bacillus
A-19685	Synovial membrane and fluid from knee joint	Diphtheroid bacillus	Diphtheroid bacillus
C-107	Synovial membrane from fusiform finger joint	No growth	Streptococcus (T.S.)
C-100	Synovial membrane from fusiform finger joint	No growth	Streptococcus (T.S.)
C-121	Synovial fluid from knee joint	Streptococcus (T.S.)	No growth

* T.S. = typical strain; S.N-H. = Streptococcus nonhemolyticus.

duration. For many years she had suffered from frequent sore throat. Physical examination showed swollen knees due to thickened synovial membrane and increase of synovial fluid. The remainder of her joints seemed free from disease at the time of examination. Fluid from the knee joint yielded a streptococcus. Two blood cultures were sterile.

A man (A-19685), aged 28, suffered from chronic infectious arthritis involving the toes, ankles, knees, spine and sacro-iliac joints of four years' duration. Physical examination showed a considerably swollen right knee, held in partial flexion. The right ankle was also swollen, with limited motion. The other joints showed no morbid changes. An arthroplastic operation was performed on the right knee, and cultures were taken from the synovial membrane and fluid. A diphtheroid bacillus was isolated in pure culture from the synovial membrane, and a blood culture was taken before the operation yielded the same organism.

A man (R-101), aged 61, presented the most interesting case in this series of patients subjected to joint cultures. He gave a history of pain and disability of both hips of ten years' duration. Physical examination showed that the left hip was ankylosed in a flexed position. The right hip had considerable limitation of motion, but was not ankylosed. A roentgenogram of the hip joints showed marked distortion and flattening of the head of the left femur, with obliteration of the interarticular space. The right side showed the same process but less advanced. The patient had one abscessed tooth, and following its extraction, he developed

pain and swelling of the left wrist. An arthroplastic operation was performed on the left hip, and cultures were made from some of the bony curettings. A streptococcus was recovered after thirteen days of incubation.

Cultures were made from the abscessed tooth and the patient's blood. From both sources there were cultivated streptococci, which were culturally and biologically identical with the organism recovered from the hip joint.

The organism isolated from the bony curettings of the hip joint was injected into a rabbit (table 8, rabbit 1). A chronic arthritis was produced, and at autopsy blood cultures from the rabbit yielded the same organism in pure culture.

Summarizing the seven cases of infectious arthritis in which cultures were obtained from arthritic joints, five of the seven yielded positive joint cultures. Four of the five positive cultures showed a streptococcus. Two of these streptococcal strains presented the appearance of hemolytic streptococci and were culturally similar to the type of streptococcus obtained in the majority of the blood cultures. The third strain was *Streptococcus viridans* and the fourth strain a nonhemolytic streptococcus. In one case, cultures from the joints yielded a pure growth of diphtheroid bacillus. It is significant that in four of the five cases with positive cultures from the joints, an organism identical in every way with the one isolated from the joint was also recovered from the blood.

CULTURAL AND BIOLOGIC CHARACTERISTICS OF THE STREPTOCOCCI ISOLATED FROM BLOOD AND JOINT CULTURES

On culture mediums, the streptococci which have been isolated from the blood and joints of patients with chronic infectious arthritis can be readily differentiated into three groups: (1) a streptococcus which presents the appearance of an attenuated *Streptococcus hemolyticus;* (2) *Streptococcus viridans;* (3) *Streptococcus nonhemolyticus,* or the so-called indifferent streptococcus. All of these streptococci have one feature in common, that is, their very slow growth in the original blood culture broth flasks. The average time of appearance of these streptococci as tested by frequent subcultures was approximately fifteen days. In some instances the flask had been in the incubator for thirty days before streptococci could be demonstrated. On the other hand, there were exceptional instances in which streptococci were isolated after four or five days of incubation. In a number of cases, when the original flask had shown no growth after thirty days of incubation, stained smears from the centrifugated sediment showed streptococci, and cultures taken from this sediment yielded streptococci.

In contrast to the original cultures, subcultures grew readily on the usual laboratory mediums. On blood agar plates, both superficial and deep colonies were usually recognizable after twenty-four hours of incubation. Subcultures in plain broth showed an abundant growth after twenty-four hours.

1. The type of streptococcus which has been encountered most frequently in the blood cultures is the organism designated as the "typical strain." It appears to be an attenuated *Streptococcus hemolyticus*. In the forty-eight patients whose blood cultures yielded streptococci, forty, or 83.3 per cent, fell into this group. Of the four strains of streptococcus isolated from arthritic joints, two fell into this group.

Fig. 2.—Smear from twenty-four hour broth culture of "typical strain" of streptococcus (no. B-30) isolated from blood culture of patient R-101. Methylene blue stain; approximately × 1000.

Morphologically, the "typical strain" is a very small gram-positive coccus, round or slightly oval, which in liquid mediums forms chains of from four to twenty cocci (fig. 2). On solid mediums, the chains are shorter. On blood agar plates, the colonies of this organism present a characteristic appearance. After twenty-four hours' incubation, deep colonies appear as minute, biconvex, grayish colonies surrounded by a hazy zone of hemolysis. The hemolytic zone is neither as clear nor as

wide as that of a typical *Streptococcus hemolyticus* colony (fig. 3). Under the microscope, a small number of red blood cells can be seen throughout the hemolytic zone surrounding the colony. There is also a small amount of methemoglobin formation visible.

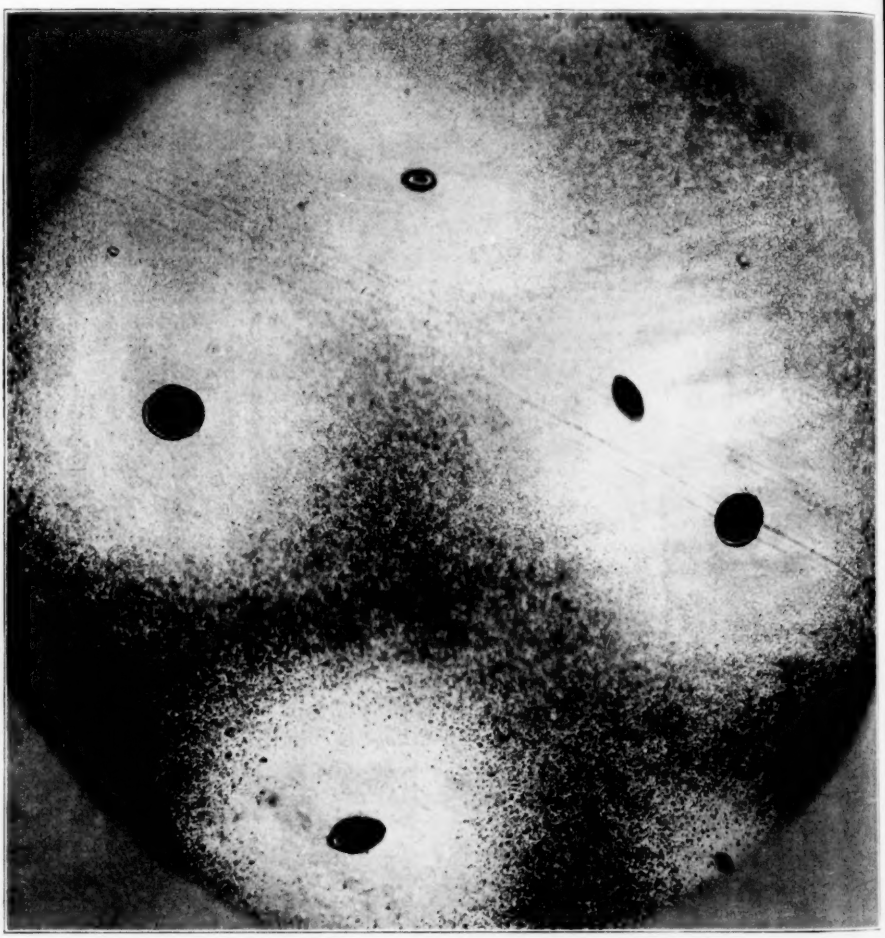

Fig. 3.—Deep colonies of "typical strain" of streptococcus number B-30 in a twenty-four hour blood-agar plate culture; approximately × 40.

Superficial colonies on blood agar plates are round, gray, flatly convex, with dull rough surfaces. By transmitted light, the superficial colony (fig. 4) is also surrounded by some hemolysis, but the colony and the surrounding zone have a slight but definite greenish tinge. The

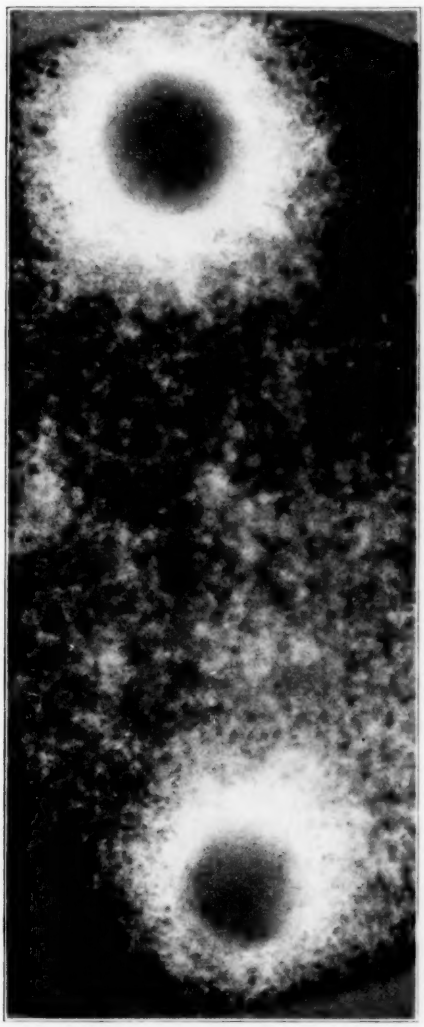

Fig. 4.—Superficial colonies of "typical strain" of streptococcus no. B-30 in a twenty-four hour blood-agar plate culture; approximately × 100.

superficial colonies are somewhat friable under the needle. When they are removed, the agar underneath is marked by a few specks of green pigment.

In blood broth, this organism grows readily with the production of a heavy granular and sometimes flocculent sediment, with slight turbidity of the medium. After twenty-four hours' incubation, a zone of hemolysis about 1 cm. in depth appears at the bottom of the tube. Complete hemolysis of the blood cells never occurs during the first twenty-four hours of incubation, but may take place after several days of incubation. Blood broth cultures show little, if any, green discoloration. This organism grows readily in plain broth, producing a considerable amount of sediment, and throughout the medium a heavy granular growth which tends to adhere to the sides of the tube.

All the "typical strains" were insoluble in bile.

2. In a second but much smaller group of patients with chronic infectious arthritis, cultures from the blood and joints yielded a type of streptococcus which differed both culturally and biologically from the typical strain just described. Altogether, the blood cultures from six patients revealed a streptococcus which on blood agar plates produced colonies surrounded by zones of methemoglobin and which corresponded in all respects with the organism usually referred to as *Streptococcus viridans*. *Streptococcus viridans* was also recovered from one of the joint cultures.

Morphologically, these green streptococci resemble the "typical strain" in being small, but in liquid mediums they tend to grow in much longer chains. On blood agar plates the colonies present the usual characteristic appearance, small, gray, opaque colonies surrounded by a light greenish zone. In blood broth these streptococci produce a luxuriant growth which tends to settle to the bottom of the tube, leaving the supernatant fluid diffusely cloudy. The broth takes on a slightly greenish tinge, but there is no hemolysis. The growth in plain broth resembles that in blood broth.

3. In three patients an indifferent streptococcus which produced no change on blood agar plates was isolated. In cases A-19244 and R-105, this organism was recovered from the blood, while in the third patient (A-1936) the streptococcus was isolated in pure culture from the knee joint. Strangely enough, the blood culture from the latter patient showed no streptococci, but diphtheroid bacilli.

These strains of indifferent streptococci form small opaque red-brown colonies on blood agar, and resemble the streptococcus described by Small [12] and by Birkhaug [21] in their studies on the etiology of rheu-

21. Birkaug, K. E.: Rheumatic Fever: Bacteriologic Studies of a Non-Methemoglobin-Forming Streptococcus with Special Reference to Its Soluble Toxin Production, J. Infect. Dis. **40**:549 (May) 1927.

matic fever. This organism has been referred to by Small as *Streptococcus cardio-arthritidis*. It should be noted that none of these three patients gave a history of rheumatic fever, nor did their arthritic manifestations resemble those of rheumatic fever.

TABLE 5.—*Fermentations Reactions and Solubility in Bile of Streptococcal Strains* *

Typical Strains	May, 1928						November, 1928				
	Inulin	Mannite	Dextrose	Lactose	Salicin	Bile	Inulin	Mannite	Dextrose	Lactose	Salicin
B-1	—	—	+	+	+	—	..	..	..	..	..
B-2	—	—	+	+	+	—	—	—	+	+	+
B-3	—	—	+	+	+	—	—	—	+	+	+
B-5	—	—	+	+	+	—	—	—	+	+	+
B-6	—	—	+	+	+	—	—	—	+	+	+
B-7	..	..	..	..	..	..	—	—	+	+	+
B-9	..	..	..	..	..	..	—	—	+	+	+
B-10	—	—	+	+	+	—	—	—	+	+	+
B-11	—	—	+	+	+	—	—	—	+	+	+
B-12	—	—	+	+	+	—	—	—	+	+	+
B-13	—	—	+	+	+	—	—	—	+	+	+
B-14	..	..	..	..	..	..	—	—	+	+	+
B-15	—	—	+	+	+	—	—	—	+	+	+
B-16	..	..	..	..	..	..	—	—	+	+	+
B-17	..	..	..	..	..	..	—	—	+	+	+
B-18	—	—	+	+	+	—	—	—	+	+	+
B-19	—	—	+	+	+	—	—	—	+	+	+
B-21	—	—	+	+	+	—	—	—	+	+	+
B-22	—	—	+	+	+	—	—	—	+	+	+
B-23	—	—	+	+	+	—	—	—	+	+	+
B-24	—	—	+	+	+	—	—	—	+	+	+
B-25	—	—	+	+	+	—	—	—	+	+	+
B-27	—	—	+	+	+	—	—	—	+	+	+
B-28	..	..	..	..	..	—	—	—	+	+	+
E-28	—	..	..	..	..	—	—	—	+	+	+
B-30	—	..	..	..	..	—	—	—	+	+	+
J-30	—	—	+	+	+	—	—	—	+	+	+
B-41	—	—	+	+	+	—	—	—	+	+	+
B-43	—	—	+	+	+	—	—	—	+	+	+
B-44	—	—	+	+	+	—	—	—	+	+	+
B-48	..	..	..	..	..	—	—	—	+	+	+
B-32	..	..	..	..	..	—	—	—	+	+	+
B-40	—	—	+	+	+	—	—	—	+	+	+
B-40′	—	—	+	+	+	—	—	—	+	+	+
B-53	..	..	..	..	..	—	—	—	+	+	+
J-46	..	..	..	..	..	—	+	+	+	+	+
Streptococcus viridans											
B-47	—	+	+	+	+	—	—	+	+	+	+
J-47	—	..	+	+	+	—	—	+	+	+	+
B-49	..	..	..	..	..	—	—	+	+	+	+
B-45	..	..	..	..	..	—	—	—	+	+	+
Streptococcus nonhemolyticus											
B-35	+	+	+	+	+	—	+	+	+	+	+
B-50	..	..	..	..	..	—	—	+	+	+	+
B-39	..	..	..	..	..	—	+	+	+	+	+

* For the sugars, + indicates acid and clot, —, neither acid nor clot; for bile, — indicates no solubility.

Sugar Fermentations.—Sugar fermentations were carried out on thirty-six of the so-called "typical strains," on four of *Streptococcus viridans* strains, and on three of the indifferent strains. Tests on five sugars were performed by two different methods at different times (table 5). In May, 1928, sugar-free broth was employed as a medium, while in November, Hiss' serum water medium was used. In both cases, litmus was added as an indicator. In both series, 0.1 cc. of a

10 per cent solution of one of the sugars was added to each tube of culture medium. At the time of the test, 0.1 cc. of a twenty-four hour sugar-free broth culture of streptococcus was added to each tube of sugar medium. The fermentation tubes were then allowed to incubate for seven days, and readings were made.

As will be seen in table 5, all of the "typical strains" with one exception acted uniformly on the sugars, fermenting dextose, lactose and salicin, and having no effect on inulin and mannite. The exceptional strain (B-46) fermented inulin and mannite as well as the other sugars. This strain was isolated from the blood of a patient with high fever and a fulminating infection. This organism on culture mediums falls in the typical group, but according to the fermentation and agglutination tests, it is biologically independent. With this one exception, the sugar reactions for the typical strains were strikingly uniform. Furthermore, the reactions obtained in November were entirely consistent with those obtained six months earlier.

Four of the *Streptococcus viridans* strains were tested on the sugars (table 5). All of the four strains fermented dextrose, lactose and salicin. Three of the four fermented mannite. They had no effect on inulin.

The three strains of *Streptococcus nonhemolyticus* fermented mannite, dextrose, lactose and salicin. Two of the three fermented inulin.

Agglutination Reactions.—In order to determine whether there was any biologic relationship between the streptococci which had been isolated from the blood and the joints of patients with chronic infectious arthritis, cross-agglutination tests were made with fifty strains (table 6). Rabbits were immunized against nine streptococci, seven of these being "typical strains" and the other two, *Streptococcus viridans.* The agglutination tests were carried out as follows:

A twenty-four hour broth culture of streptococcus was killed by heating the culture at 56 C. for one hour. The sediment from 10 cc. of the killed culture was then injected intravenously into a large rabbit. These injections of killed streptococci were repeated at five day intervals for six weeks. Ten days after the last injection, the rabbit was bled and the serum tested for agglutinins. If the rabbit serum did not show an agglutination titer of at least 1:1,280 against the homologous streptococcus, the rabbit was given further injections of killed organisms.

The antigens for the agglutination tests were prepared by growing the streptococci in potato broth for eighteen hours. By using this medium, a diffuse growth was obtained in the majority of cases. In the case of those strains that gave a granular growth in potato broth, a diffuse growth was obtained by transplanting the culture several times in plain broth before cultivating them in the potato broth. Before performing the tests, the potato broth cultures were shaken vigorously for a minute or two, and then allowed to stand for a half hour. The upper portion of the culture was then removed for the agglutination test; 0.5 cc. of the antigen was

mixed with 0.5 cc. of the various dilutions of immune rabbit serum. The agglutinations were carried out to a titer of 1:1,280.

As controls, rabbit serum withdrawn before immunization was tested against the streptococci. Another control consisted of 0.5 cc. of sterile broth and 0.5 cc. of the culture. The agglutination tubes were left for two hours in the water bath

TABLE 6.—*Titer of Agglutination Reactions with Serums of Rabbits Immunized Against Seven "Typical" Streptococcus Strains and Two Streptococcus Viridans Strains*

Organisms	Serum T.S. B-2	Serum T.S. B-5	Serum T.S. B-6	Serum T.S. B-18	Serum T.S. B-22	Serum T.S. B-27	Serum T.S. E-28	Serum S.V. B-38	Serum S.V. B-47
T.S.* B-1	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T.S. B-2	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S. B-2′	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T.S. B-3	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T.S. B-5	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	80
T.S. B-6	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T.S. B-6′	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S. B-7	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T.S. B-9	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T.S. B-10	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S. B-11	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T.S. B-12	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T.S. B-12′	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	20
T.S. B-13	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	20
T.S. B-14	1,280	1,280	1,280	1,280	1,280	1,280	1,280	40	20
T.S. B-15	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S. B-16	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	20
T.S. B-17	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S. B-18	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	40
T.S. B-19	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S. B-21	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	40
T.S. B-22	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T.S. B-23	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T.S. B-24	1,280	1,280	1,280	1,280	1,280	1,280	1,280	80	0
T.S. B-25	1,280	1,280	1,280	1,280	1,280	1,280	1,280	40	0
T.S. B-27	1,280	1,280	1,280	1,280	1,280	1,280	1,280	80	20
T.S. B-28	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S. E-28	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S. T-28	80	160	160	160	160	80	40	40	0
T.S. B-30	1,280	1,280	1,280	1,280	1,280	1,280	1,280	40	0
T.S. J-30	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	0
T.S.Te-30	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	0
T.S. B-40	1,280	.....	1,280	.....	.....	1,280	1,280	40	20
T.S. B-40′	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	20
T.S. B-40″	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T.S. T-40	320	640	320	640	640	320	.....	..	40
T.S. B-41	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	80
T.S. B-43	1,280	1,280	1,280	1,280	1,280	1,280	1,280	80	0
T.S. B-44	1,280	1,280	1,280	1,280	1,280	1,280	1,280	20	40
T.S. B-48	1,280	1,280	1,280	1,280	1,280	1,280	1,280	0	20
T.S. J-53	.....	.....	.....	.....	.....	.....	1,280	..	..
T.S. B-32	80	80	80	80	80	80	.....	..	80
T.S. B-46	0	0	0	0	0	0	0	0	0
S.V. B-47	20	20	40	40	80	20	20	20	1,280
S.V. J-47	20	40	20	80	80	40	20	80	1,280
S.V. B-36	20	80	40	80	40	40	0	1,280	640
S.V. B-45	20	80	20	80	80	40	20	160	20
S.V. B-49	40	80	160	160	160	40	40	320	160
S.N-H. B-35	0	0	0	0	0	0	0	0	0
S.N-H. B-50	..	..	..	..	..	..	0	..	..
Controls									
S.V.	40	80	20	40	40	20	20	80	80
S.H.	0	0	0	0	0	0	0	0	0
S.N-H.	0	0	0	0	0	0	0	0	0

* T.S. = "typical strain"; S.V. = Streptococcus viridans; S.N-H. = Streptococcus nonhemolyticus.

For the agglutination tests, the following dilutions of serums were used: 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280. The figures in the table indicate the limit of agglutination with these dilutions; 0 = no agglutination.

The controls were stock cultures of streptococci obtained from sources other than arthritis. B = blood, J = joint, T = tonsil, Te = Teeth, E = erythema bullosa.

at 56 C. They were then placed in the refrigerator and readings were made the following morning.

Cross-agglutination tests were carried out with the nine immune serums, testing them against forty-three of the "typical strains" and seven of the atypical strains. As will be seen in table 6, thirty-seven of the forty-three "typical strains" were agglutinated in dilutions as high as 1:1,280 by all seven of the serums of rabbits immunized against the "typical strain." One strain (B-32) agglutinated only to a dilution of 1:80, and one strain (B-46) did not agglutinate with any of the immune serums. As pointed out under the fermentation tests, strain B-46 was isolated from the blood stream of a patient with septic arthritis. This organism showed no biologic relationship to the other typical strains. Two strains, T-28 and T-40, were isolated from excised tonsils and were agglutinated by the immune serums of typical strains as high as 1:160 and 1:640, respectively.

One of the most interesting facts brought out by these agglutination reactions was the close biologic relationship between the "typical strains" isolated from the different foci in the same patient. For example, B-28 was recovered from the blood stream, E-28 from an erythematous bulla and T-28 from the center of an excised tonsil of the same patient. These three strains, culturally identical, were agglutinated by all the antiserums of the typical strains. B-30 was isolated from the blood, J-30 from a joint and Te-30 from a root abscess in the same patient. All three strains showed high agglutination with the antiserums of the typical strains of streptococci. B-40 was isolated from the blood and T-40 from the tonsils of the same patient. Both strains showed high agglutination with the antiserums of the typical strains. When repeated blood cultures on the same patient showed streptococci, these streptococci were agglutinated equally well by the immune serums.

In contrast to the high agglutinations with the serums of typical strains, the typical strains showed little or no agglutination with the two *Streptococcus viridans* serums. Furthermore, *Streptococcus viridans* strains showed little or no agglutination with the serums of the seven typical strains. They naturally gave high agglutination readings with the homologous *Streptococcus viridans* serums.

The two strains of *Streptococcus nonhemolyticus* (B-35) and (B-50) showed little or no agglutination with either the serums of typical strains or the serums of *Streptococcus viridans* strains.

In addition to these tests, the nine immune serums were tested against three control strains of streptococci. The control *Streptococcus viridans* and the control *Streptococcus hemolyticus* strains had both been isolated from the sputum of patients who showed no symptoms of arthritis. (*Streptococcus nonhemolyticus* was supplied to us by Dr. James Small of Philadelphia.) All of the immune serums produced a

slight agglutination of the control *Streptococcus viridans*, but had no effect whatever on either *Streptococcus hemolyticus* or *Streptococcus nonhemolyticus*.

Absorption Tests.—Absorption tests were carried out with three of the typical strain serums against fifteen of the typical strains and two *Streptococcus viridans* strains as follows:

The sediment from 50 cc. of a twenty-four hour broth culture of streptococcus was mixed with a 1:4 dilution of the immune serum. The mixture was shaken for three minutes and put in the water bath for two hours at 37 C. It was then allowed to stand in the icebox over night. In the morning, the mixture was centrifugated and the supernatant serum removed. Agglutination tests were set up in the same dilutions as those used in the original agglutination tests. Controls

TABLE 7.—*Absorption Tests* *

Degree of Agglutination of Streptococcal Strains with Serums from Three Immunized Rabbits before and after Absorption of Agglutinins.

	Strain B-6			Strain B-2			Strain E-28		
Antigen, Typical Strains	Absorbed Immune Serum	Unabsorbed Immune Serum	Normal Serum	Absorbed Immune Serum	Unabsorbed Immune Serum	Normal Serum	Absorbed Immune Serum	Unabsorbed Immune Serum	Normal Serum
B-6	0	1,280	0	0	1,280	0	0	1,280	0
B-2	0	1,280	0	0	1,280	0	0	1,280	0
E-28	0	1,280	0	0	1,280	0	0	1,280	0
B-22	0	1,280	0	20	1,280	0	0	1,280	0
B-15	0	1,280	0	0	1,280	0	0	1,280	0
B-3	0	1,280	0	0	1,280	0	0	1,280	0
B-13	0	1,280	0	0	1,280	0	20	1,280	0
B-9	0	1,280	0	0	1,280	0	0	1,280	0
B-30	0	1,280	0	0	1,280	0	0	1,280	0
B-24	0	1,280	0	0	1,280	0	0	1,280	0
B-17	0	1,280	0	0	1,280	0	0	1,280	0
B-25	0	1,280	0	0	1,280	0	20	1,280	0
B-27	0	1,280	0	0	1,280	0	0	1,280	0
B-14	0	1,280	0	0	1,280	0	0	1,280	0
B-11	0	1,280	0	0	1,280	0	20	1,280	0
Strep. vir. strains									
B-49	..	..	..	40	40	0	..	.....	0
B-47	40	40	0	40	40	0	..	.....	..

In the absorption tests, the following dilutions of serums were used for the agglutination reactions: 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280. The figures in the table indicate the limit of agglutination with these dilutions; 0 = no agglutination.

were carried out with unabsorbed serum and normal rabbit serum. All the tubes were put in the water bath at 56 C. for two hours, then in the icebox over night. Readings were made on the following morning.

As will be seen in table 7, there was almost complete absorption by all the fifteen typical strains. In tests for *Streptococcus viridans*, the readings were the same as before the absorption tests were performed.

RELATION OF STREPTOCOCCI RECOVERED FROM THE BLOOD TO STREPTOCOCCI ISOLATED FROM JOINTS AND FROM FOCI OF INFECTION

An interesting phase of this investigation has been the correlation of the streptococci isolated from the blood with streptococci cultivated from the joints and from various foci of infection. Several cases will now be cited.

A man (A-11301), aged 49, had pain and stiffness in the feet, knees, right elbow, shoulders and back of two years' duration. The results of physical examination of the joints were essentially negative. The tonsils were moderately enlarged and infected. Cultures were made from the patient's blood on three different occasions, and each time a streptococcus of the typical strain was isolated in pure culture. All three strains were biologically identical. A streptococcus recovered from the excised tonsils was culturally similar to the streptococcus isolated from the blood, and it was agglutinated by serums of "typical strains" in dilution as high as 1:640 (table 5, B-40, B-40′, B-40″ T-40).

A woman (A-94403), aged 23, gave a history of pain and swelling of the knees and fingers, of one month's duration. Physical examination revealed an early case of chronic infectious arthritis with beginning fusiform fingers. Both knees were slightly swollen and tender. The patient had numerous erythematous bullae on both legs. The tonsils were small, cryptic and diseased. Cultures were made from the patient's blood, from the excised tonsils and from fluid aspirated from the bullae. From each source a streptococcus of the "typical strain" was isolated, and all three strains were morphologically and culturally identical (table 6, B-28, E-28, T-28). The streptococcus isolated from the tonsils was agglutinated by serums of "typical strains" as high as 1:160. The streptococcus isolated from the bullae was agglutinated by the serums of typical strains as high as 1:1,280.

In case R-101 (complete protocol in section on joint cultures) there were "typical strains" of streptococcus in cultures from the blood, from the hip joints and from a root abscess. The streptococci from all three sources were agglutinated by serums of typical strains as high as 1:1,280 (table 6, B-30, J-30, Te-30).

These three protocols furnish evidence that in patients with chronic infectious arthritis, foci of infection may harbor a streptococcus culturally and biologically identical with the strain of streptococcus isolated from the blood or joint. Comparatively little attention has been devoted to this phase of our problem, but we hope to investigate it more thoroughly in the future.

EXPERIMENTAL ARTHRITIS

Several of the strains of streptococcus which have been isolated from the blood and joints of patients with chronic infectious arthritis have been injected into various laboratory animals with the idea of determining the virulence of these organisms and also their capacity to produce an experimental arthritis. The typical strains differ somewhat in their virulence for mice, some killing a mouse in doses of 0.5 cc. of broth culture, while others produced little or no effect. The typical strain is fairly virulent for rabbits; 5 cc. of broth culture intravenously usually kills the animal in forty-eight hours. On the other hand, doses as large as 10 cc. intravenously produce no symptoms in a ringtail or a rhesus monkey.

Experimental Arthritis.—Eleven rabbits were given intravenous injections of streptococci which had been isolated from the blood of patients with arthritis (table 8). Ten of these received some one of the typical strains, and the eleventh received *Streptococcus viridans.* Of

TABLE 8.—*Resumé of Rabbit Experiments*

Number of Rabbit	Weight, Gm.	Strain of Streptococcus Injected	No. of Injections Before Arthritis Appeared	Total Number of Injections	Joints Affected	Duration of Arthritis	Loss of Weight, Gm.	Blood Culture*	Joint Culture	Lesions in Heart	Remarks
1	2,800	B-30	8	10	Interphalangeal, elbows	2 mo.	910	Strept. T.S.	—	None	
2	3,880	E-28	17	18	Knees, left elbow, shoulders...	3 mo.	660	Strept. T.S.	—	None	Died of pneumonia
3	1,250	B 27	4	4	Interphalangeal, elbows	4 wk.	260	Strept. T.S.	Strept. T.S.	None	
4	1,550	J-47	4	23	Left wrist, left elbow.....	6 wk.	150	Negative	Negative	—	Animal gradually recovered
5	2,100	B-5	4	6	Wrists, right elbow.....	6 wk.	80	—	Strept. T.S.	None	
6	1,275	B-2	6	12	Right elbow, right wrist.....	2 mo.	70	Strept. T.S.	Strept. T.S.	None	
7	950	B-12	..	1	None	—	—	—	—	None	Died 24 hours after injection
8	1,720	B-21	2	3	Interphalangeal, left knee, right elbow	3 wk.	120	Strept. T.S.	Strept. T.S.	None	
10	1,120	B-36	..	5	None	—	10	—	—	None	Died 3 weeks after last injection
12	2,500	B-46	..	4	None	—	500	—	—	None	Died 2 weeks after last injection
27	1,950	B-40	..	1	None	—	—	—	—	None	Died 24 hours after injection

* Strept. T.S. = typical strain of streptococcus.

the eleven rabbits, seven developed arthritis in one or more joints, while the remaining four failed to show symptoms (table 8).

The usual mode of procedure was as follows:

A broth culture of streptococcus was centrifugated and the sediment resuspended to the original concentration in saline. The initial dose was from 0.5 to 1 cc. intravenously. Injections were repeated at intervals of from three to five days, the dose being increased each time. The maximum dose was 5 cc. In none of the rabbits were symptoms noted after the first or second injections. Symptoms in the joints usually appeared after the fifth or sixth injection; in one rabbit, however, arthritis did not appear until after the seventeenth injection.

The only abnormal signs noted in the affected rabbits were limping and loss of weight. On examination, the affected joints were swollen and tender. Various joints were involved. Because of the frequent involvement of the interphalangeal joints of man, it was particularly interesting to note the frequent involvement of the interphalangeal joints of the rabbits. One or both elbows were involved in all seven cases, the knees in two cases and the wrist in two cases. The shoulder joint was involved only once.

Six of the seven rabbits eventually died after running a course of from two and one half to nine months. The remaining rabbit recovered completely from the disease in spite of repeated injections of streptococci.

At autopsy, all the rabbits were found to have lost considerable weight. The affected joints were swollen, and, when the joints were opened, a slightly cloudy, mucoid fluid presented itself. The periarticular tissues appeared thicker than normal, and the synovial membrane was congested. The internal organs appeared normal. The condition of the heart was noted particularly with regard to vegetative endocarditis. No vegetations were observed in any of the rabbits.

Bacteriologic study of these arthritic rabbits resulted in observations similar to those obtained in the human patient. Blood cultures were taken of six of the affected rabbits, and in five of the six animals a streptococcus morphologically and culturally identical with the organism injected was recovered from the blood. The blood cultures were taken from five to thirty days after the last intravenous injection of streptococci. One rabbit (no. 2) showed a positive blood culture thirty days after the last intravenous injection. The organism did not appear in the blood culture flasks until after ten days of incubation.

In five of the seven rabbits with arthritis, fluid from one of the affected joints was cultured, and a streptococcus morphologically and culturally identical with the organism injected was recovered from the synovial fluid in four cases.

Microscopic sections through the affected joints presented a variable picture, depending on the duration of the arthritis. In cases of only a few weeks' duration, the interarticular space contains mucus and broken-down cells and sometimes a considerable number of leukocytes. There may be some superficial necrosis of the cartilage, and the synovial membrane is thickened and infiltrated with leukocytes and plasma cells. Many large endothelial cells are noticed. Rabbits in which the arthritis has existed for several months show changes of a more chronic nature. There is less exudate in the joint cavity, and the synovial membrane takes on the appearance of chronic granulation tissue, the deeper part being composed of newly formed connective tissue, and the superficial part rich in cellular elements. The leukocytes are mostly lymphoid and plasma cells, together with a large number of macrophages, which appear to be undergoing transition into fibroblasts.

Summarizing the pathologic changes in these joints, it may be said that in the experimental arthritis produced by the typical human strain of streptococcus, the histologic sections show a gradual transition from a stage of fairly acute inflammation to a subacute or chronic condition with considerable new formation of fibrous tissue.

When sections from one of the affected joints of a rabbit with chronic arthritis (fig. 5) are compared with sections from a fusiform finger in man (fig. 6), a striking similarity is seen in the two pictures. Indeed, without some method of identification, it would be impossible to tell which section came from the rabbit and which from the human lesion.

The following protocols illustrate the pathologic changes in a rabbit with experimental arthritis and in a patient with chronic infectious arthritis.

A belgian hare, rabbit 1, weighing 2,265 Gm., was injected intravenously twice weekly (Nov. 24, 1927, to March 1, 1928) with broth cultures of a "typical strain" of streptococcus isolated from the bony curettings of the patient in case R-101 (see protocol under joint cultures). The dose of culture ranged from 0.5 to 2 cc. The animal gradually lost weight, and on Jan. 23, 1928, the first symptoms of arthritis were noted in the knees. They were slightly swollen, and the animal limped. On February 22, the elbows became swollen, the right more than the left. The condition of the knees gradually cleared up, and at the time of death on March 30, they did not show any swelling.

At autopsy, the elbows were both distinctly swollen, but there was no definite evidence of arthritis in any other joint. The internal organs were entirely negative. The heart showed no pathologic changes. Blood taken from the heart shortly before the death of the animal gave a positive culture of a typical strain of streptococcus identical with the one injected. The joint culture was negative.

Microscopic sections through one of the elbows showed the following changes (fig. 5): The synovial membrane was considerably thickened and presented the appearance of chronic inflammatory tissue. The endothelial lining had been almost completely replaced by a thin layer of necrotic tissue, which at some points contained numerous leukocytes, mostly of the lymphoid type. Beneath the layer of

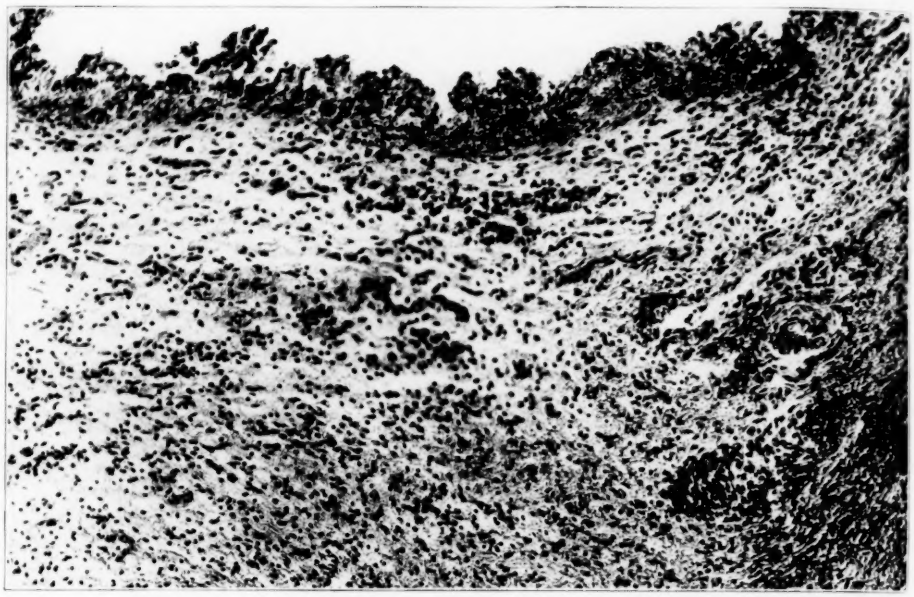

Fig. 5.—Microscopic section of synovial membrane from elbow of rabbit 1 with experimental arthritis produced by "typical strain" of streptococcus B-30; hematoxylin-eosin stain; reduced from an approximate magnification of × 140.

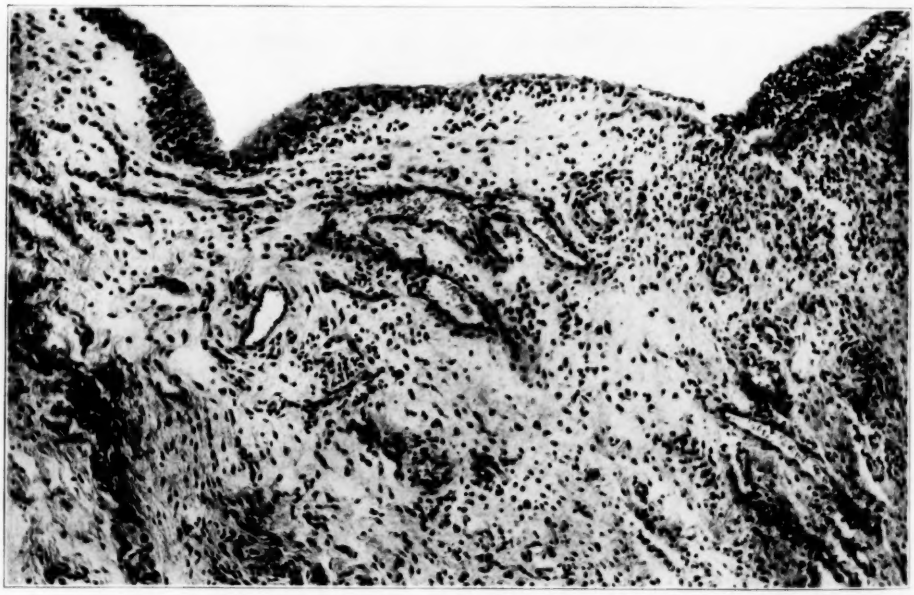

Fig. 6.—Microscopic section of synovial membrane from a fusiform finger of patient C-107. Note the superficial necrosis and dense infiltration of leukocytes near the right margin. Hematoxylin-eosin stain; reduced from an approximate magnification of × 140.

necrosis, there was a thick zone of loose connective tissue infiltrated at many points with leukocytes and plasma cells. The leukocytes were mostly of the lymphoid type, although polymorphonuclear leukocytes were also present. Plasma cells were abundant. Areas of hyaline degeneration occurred at some points in the connective tissue.

A woman (C-107), aged 32, came in with a history of pain and swelling of the joints of four years' duration. Symptoms first developed in the fourth toe of the right foot. Shortly after this, symptoms appeared in the spine and fingers. The elbows and wrists recently became involved. Physical examination showed several fusiform fingers and swelling of both wrists. Each of two blood cultures yielded the "typical strain" of streptococcus. Cultures were taken from a piece of synovial membrane removed from one of the fusiform fingers, but no organisms were recovered.

Microscopic section through the synovial membrane showed a vascular and rather loose connective tissue, infiltrated with lymphoid and plasma cells and a moderate number of polymorphonuclear leukocytes. The endothelial lining in some places was normal. At other points the endothelial cells were piled up and stratified. At still another point the tissue showed extensive necrosis and over this area the epithelium had been entirely destroyed and its place taken by a layer of polymorphonuclear leukocytes. In the deeper parts, the tissue showed areas of hyaline degeneration. The section presented the typical picture of chronic granulation tissue.

Figure 5 is a photomicrograph of a section from the elbow of rabbit 1, and figure 6 a photomicrograph of a section from the synovial membrane in case C-107. The similarity of the tissue changes in the two sections is striking.

COMMENT

In the early part of this article we have shown what confusion has existed in the minds of investigators concerning the etiology of chronic arthritis. Furthermore, we have pointed out that even among bacteriologists who have at times obtained positive cultures from the blood or from the joints of arthritic patients, there has been marked discrepancy in the results obtained. It was because of this confusion and doubt as to the etiology of the disease that the present study was undertaken.

Altogether, seventy-eight patients with chronic infectious arthritis have been subjected to blood cultures. Of these seventy-eight cases, forty-eight, or 61.5 per cent, yielded a streptococcus. Of the forty-eight strains of streptococcus isolated from blood cultures, forty, or 83.3 per cent, were found to be culturally and biologically identical and presented the appearance of attenuated hemolytic streptococci. Of the eight remaining strains, six were classified as *Streptococcus viridans*, two as *Streptococcus nonhemolyticus*. In this report the predominant strain has, for lack of a better name, been referred to as the "typical strain." In the earlier part of our work, we were disposed to look on this dominant organism as an atypical *Streptococcus viridans* because of its capacity to produce some green coloration on blood agar plates.

However, after several generations on artificial mediums, the typical strains all showed definite hemolytic properties, not so marked as typical *Streptococcus pyogenes,* but sufficient to produce a zone of hemolysis on blood agar plates and considerable reddening in blood broth. Furthermore, the reactions of the "typical strains" on sugars were consistent and corresponded to those of the beta type of streptococcus. Our hesitancy in classifying this organism was not dispelled when we sought the opinion of several bacteriologists. One called it streptococcus alpha prime (a subvariety of *Streptococcus viridans*); two considered it *Streptococcus hemolyticus;* while a fourth was unwilling to express a positive opinion. Dr. J. Howard Brown, who has had a large experience with streptococci, wrote:

> In spite of the slight evidence of methemoglobin formation, I think I would regard these streptococci as of the beta type because there is no real zone of methemoglobinized corpuscles next to the streptococcus colonies. This is also substantiated by the fact that serum broth cultures produce complete hemolysis of washed rabbits' cells in less than two hours.

We are very much disposed to accept Dr. Brown's opinion and call this "typical strain" *Streptococcus hemolyticus.* However, in view of the divergence of opinions, it seems wiser to suspend final judgment until the organism has received further study and to refer to it for the present as the "typical strain."

The fact that in our experience 83 per cent of the streptococci isolated from the blood of patients with chronic infectious arthritis have fallen into one biologic group, strongly supports the theory that a considerable proportion of all cases of chronic infectious arthritis are caused by a biologically specific strain of streptococcus. The comparatively small remainder of cases appears to be referable to either *Streptococcus viridans* or *Streptococcus nonhemolyticus.* It should not be forgotten that rarely a clinical syndrome indistinguishable from chronic deforming arthritis can be produced by the gonococcus.

Our investigations into the bacteriology of the joints in chronic infectious arthritis have not been as extensive as the blood cultures, but the isolation of streptococci from a number of joints would indicate that the joint lesions in this disease are actual infections. The interesting theories propounded by Swift,[22] and more recently by Zinsser,[23] as to the allergic nature of the joint lesions in rheumatic fever may or may not be applicable to chronic infectious arthritis. The latter disease appears

22. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci, Tr. A. Am. Phys. **43**:192, 1928.

23. Zinsser, H., and Yu, H.: The Bacteriology of Rheumatic Fever and the Allergic Hypothesis, Arch. Int. Med. **42**:301 (Aug.) 1928.

to have its perfect analogue in gonococcal arthritis, an infectious disease in which a primary gonococcal focus of infection in the prostate or seminal vesicles produces lesions in the joints by metastatic infection through the blood stream.

In the small series of joint cultures studied, the results were consistent with those obtained from blood cultures. The "typical strain" of streptococcus was isolated from the joint in two cases, *Streptococcus viridans* in one case and a nonhemolytic streptococcus in one. In two of the four cases with positive joint cultures, a streptococcus identical with the one isolated from the joint was also recovered from the blood.

To our minds, one of the most significant features of this study has been the correlation of streptococci isolated from a focus of infection with streptococci recovered from the blood or from the joints of the same patient. In several instances, the identity of these streptococci has been clearly proved by the similarity of their cultural and biologic reactions.

Our studies on experimental arthritis in animals are still in the preliminary stage. Several interesting facts have already been brought out. It is comparatively easy to produce a chronic nonsuppurative arthritis in rabbits with the "typical strain" of streptococcus. In rabbits with experimental arthritis, the "typical strains" can be recovered from the blood and from the infected joints. Finally, the histologic changes which take place in the joint of a rabbit with experimental arthritis are strikingly similar to those which occur in the joint of a patient with chronic infectious arthritis. When, in a patient with typical chronic infectious polyarthritis, a biologically specific strain of streptococcus has been isolated from the tonsils, from the blood stream and from one of the infected joints, when this streptococcus isolated from the patient produces similar lesions in the joints of rabbits, and when the same organism is recovered from the blood stream and from the affected joints of the rabbit, it is hard to avoid the presumption that this streptococcus is the cause of the disease.

A diphtheroid bacillus was recovered from the blood in four patients with chronic infectious arthritis, and in one of the four a diphtheroid was removed from an infected joint. This organism has been isolated by other bacteriologists from the blood and joints of arthritic patients. We are not disposed to attach much significance to its presence. Diphtheroids have been found so frequently in lymph glands of both healthy and diseased patients that their occasional presence in the blood or even in the joint would not be surprising.

Micrococcus zymogenes was isolated from the blood of two patients with chronic infectious arthritis. We are not prepared to express an opinion as to the etiologic significance of this organism at the present time.

A considerable number of the patients in this series have been treated with autogenous or stock streptococcus vaccines. In many cases the results have been encouraging; furthermore, in a number of instances, inoculations with vaccine appear to have sterilized the blood stream. Sufficient time, however, has not yet elapsed to permit of a final judgment as to the therapeutic value of vaccine.

Perhaps a few suggestions should be offered to any who may undertake a study of the bacteriology of the blood and joints in chronic infectious arthritis. The following points are all essential for successful results:

1. Select the proper type of patient. Patients with polyarthritis with swelling of several joints, preferably with one or more fusiform fingers, give the highest proportion of positive blood cultures.

2. Take plenty of blood, from 20 to 30 cc., for the blood culture.

3. Take several blood cultures on each patient, preferably after the joints have had some exercise.

4. A p_H of 7.6 is the optimum for the blood cultures.

5. The original cultures must be kept under observation in the incubator for at least four weeks, subcultures being taken every four or five days during this period. Before finally discarding the original broth flasks, some of the medium should be centrifugated and cultures and smears made from the sediment.

If, as appears highly probable from this study, chronic infectious arthritis is usually a streptococcus infection, what shall be said of the etiology of hypertrophic or degenerative arthritis? For some time there has been a growing conviction among many students of arthritis that degenerative arthritis is not a truly inflammatory process and that it is noninfectious in nature. Such a conception of degenerative arthritis is supported by the results of this study. All the blood cultures taken from patients with degenerative arthritis were sterile. Unfortunately, no opportunity for taking joint cultures on these patients presented itself. At the present time all the evidence at hand points to the conclusion that degenerative arthritis is just one more phase of the somatic deterioration which we call old age.

Some writers on arthritis have attempted to make a distinction between chronic infectious arthritis and arthritis deformans. The presence of streptococci in the blood and joints of both these clinical types would seem to indicate that there is no basis for such a distinction. Certainly from our own studies we are forced to conclude that arthritis deformans is nothing more than the end-result of chronic infectious arthritis. The "deformans" type usually presents a history of long standing.

CONCLUSIONS

1. A streptococcus can frequently be isolated from the circulating blood of patients with chronic infectious arthritis (61.5 per cent in this series of seventy-eight cases).

2. Of these streptococci, 83.3 per cent are culturally and biologically identical, and appear to be attenuated hemolytic streptococci. This dominant strain has been referred to as the "typical strain." The remaining strains fall definitely into either the viridans or the indifferent group of streptococci.

3. A streptococcus, culturally and biologically identical with the strain isolated from the blood, can sometimes be cultivated from one of the affected joints in the same patient.

4. A streptococcus, culturally and biologically identical with the strain isolated from the blood and joints, can sometimes be isolated from a focus of infection in the same patient.

5. When the "typical strain" of streptococcus is injected intravenously into rabbits, a majority of the rabbits develop a chronic nonsuppurative polyarthritis. Microscopically, the histologic changes in the rabbit's joints are practically identical with those observed in the joints of patients with chronic infectious arthritis.

6. Cultures from the blood and from the joints of rabbits infected with experimental arthritis frequently yield a streptococcus identical with the strain originally injected.

7. These observations tend strongly to confirm the theory that chronic infectious arthritis is a streptococcal infection, caused in a large proportion of cases by a biologically specific strain of this organism. The presence of this specific strain of streptococcus in the blood of several patients with advanced arthritis deformans goes far to corroborate the view already widely held that arthritis deformans and chronic infectious arthritis are one and the same disease.

CLINICAL SIGNIFICANCE OF PREMATURE BEATS

WITH PARTICULAR REFERENCE TO HEART RATE *

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The relationship that premature beats bear to prognosis is a question that has called forth many and varied opinions. There are, on the one hand, those who have considered them to be entirely benign and, on the other hand, those who have thought them evidence, in every case, of underlying cardiac disease. Between these two extremes their clinical moment is appraised in various gradations of severity. Long before the advent of the modern methods of studying arrhythmia and the recognition of the several different types of this condition, it was recognized by some that premature beats, or pulse intermittence as they were then termed, were not always to be interpreted in a serious light. There is still so much uncertainty about the significance of premature beats under varying conditions that new information based on more than impressions is highly desirable. Such information regarding the significance of premature beats at varying heart rates is herewith recorded.

LITERATURE

Although the earliest medical literature in Greek and Roman times mentioned intermittence of the pulse rate, there was not a clear separation between its significance and that of the other types of arrhythmia. In general, Galen regarded irregularity of the pulse rate as a bad sign, and all through the Middle Ages Galen's views held sway.

Heberden,[1] however, writing in 1782, said, "Some books speak of intermitting pulses as dangerous signs, but I think without reason, for such trivial causes will occasion them that they are not worth regarding in any illness unless found with other bad signs of more moment." In 1884, Richardson [2] quoted from an article he had written in 1868, in which he said that although he could not find an author who had made a special study of intermittency, he himself believed that, "In

* Submitted for publication, Sept. 11, 1928.

* From the Cardiac Clinic and Laboratory of the Massachusetts General Hospital.

1. Heberden, W.: Commentaries on History and Cure of Diseases, London, 1782.

2. Richardson, B. W.: Intermittency of the Heart and Circulation, Aesclepiad, London, **1**:193, 1884.

itself, when it is not present to an exaggerated degree, (it) is often less dangerous than it seems." He based this opinion on its common occurrence after middle age and on the long duration of life of many who present intermittency. He mentioned one patient who died at the age of 86 and was first known to have had an irregular pulse rate at 42. Interestingly too, he noted that alcohol quickens the pulse and causes the intermittency to disappear, which is later followed by a slowing, at which time it is more pronounced. He mentioned also that he had, in the treatment of intermittency, sometimes combined quinine with opium with marked benefit.

Several other cases have been recorded in which premature beats have been present for many years. Thus, Mackenzie [3] cited the case of a man in whom he noted auricular premature beats at the age of 69. They were first discovered when the patient was 18, at which time he was rejected for an appointment to India on account of the irregularity. During many of the intervening years he had been forced to earn his livelihood by work that entailed great bodily strain, and had been much depressed at times by the grave prognostications of his medical advisers, who led him to believe that his end might come at any moment. He was in fairly good health when seen by Mackenzie after fifty-one years with premature beats. Grassmann [4] reported a case in which they were known to be present for sixty-seven years, Koppang [5] one of thirty years' duration, Walsh [6] one of forty years', and Shultze [7] quoted the observation of Erb who noticed them in himself at the age of 29. They continued and for twenty-seven years he had no impairment of health. After this for seven years he had attacks of tachycardia, but these did not disturb his work or mountain climbing. At 73 he survived a grave operation on the gallbladder and died at the age of 83 from infectious enteritis. Allan [8] and Brown,[9] among others, likewise wrote that premature beats are compatible with long life.

Some authors have looked on premature beats as being largely due to the effects of the nervous system. Kaufmann and Rothberger [10]

3. Mackenzie, James: Diseases of the Heart, London, Oxford University Press, 1913.

4. Grassmann, Karl: Zur prognostischen Wertigkeit und Behandlung der praktisch-wichtigsten Herzarrythmien, München. med. Wchnschr. **67**:5, 1920.

5. Koppang, N.: Ueber Extrasystolie, Ztschr. f. ärztl. Fortbild. **21**:63, 1924.

6. Walsh, J. J.: Prognosis in Functional Heart Disease: The Story of Forty Years of Premature Systole, Internat. Clin. **4**:158, 1926.

7. Schultze, F.: Zur Frage der praktischen Bedeutung und der Behandlung der Extrasystolie, Deutsche med. Wchnschr. **50**:1357, 1924.

8. Allan, G. A.: Defects in Cardiac Rhythm in Relation to Cardiac Failure, Glasgow M. J. **95**:333, 1921.

9. Brown, W. L.: The Irregular Heart, Med. Rev. **16**:1, 1913.

10. Kaufmann, R., and Rothberger, C. J.: Ueber Extrasystolische Pulsarhythmien, Wien. klin. Wchnschr. **33**:599, 1920.

stated that they are almost always dependent on extracardiac nerve stimulation, particularly vagal. Cautley [11] said they are not a cardiac but a nervous symptom; Hoffmann [12] thought that they may arise from pure nervous and psychic causes as well as from high blood pressure. Many have regarded premature beats as being of little, if any, significance in themselves and have expressed the belief that the prognosis in any case must be based on the accompanying or underlying cardiac conditions.[13] Similarly, Bass,[14] writing of premature beats in childhood, stated that premature beats of toxic origin including those which occur in rheumatic fever are not necessarily a symptom of permanent injury.

Lewis [15] has been a little more guarded in his views. He believed that although premature beats in themselves cannot be regarded as evidences of serious involvement of the heart muscle, still they constitute and bear witness to defects, and single ones may be the precursors of grave conditions. Grassmann [4] was of the opinion that long observation of the case is necessary for prognosis, and Babcock [16] believed that in the course of time they have harmful effects. Reilly [17] stated that

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11. Cautley, Edmund: Irregularity of the Heart, St. Barth. Hosp. Rep. **29**: 283, 1893.

12. Hoffmann, A.: Ueber die Enstehung der Extrasystolen Irregularität, München. med. Wchnschr. **53**:1987, 1906.

13. Mackenzie, J.: Some Manifestations of the Healthy Heart in the Young Frequently Taken as Indications for Treatment, Brit. M. J. **2**:1697, 1912. Lohman, W. H.: The Diagnosis, Prognosis and Treatment of Common Disturbances of Cardiac Rhythm, Long Island M. J. **9**:361, 1915. Griffith, T. W.: Discussion on Cardiac Irregularities Especially in Reference to Prognosis and Treatment, Brit. M. J. **2**:697, 1924. Greiwe, J. E.: Premature Ventricular Systoles: Their Clinical Significance, J. A. M. A. **67**:1072 (Oct. 7) 1916. Price, F. W.: Recent Advances in the Diagnosis, Treatment and Prognosis of Heart Disease, Brit. M. J. **1**:477, 1913. Maldague, L.: L'extrasystolie, Rev. méd. de Louvain **25**:289, 1909. Leyden, E.: The Prognosis of Diseases of the Heart, Woods Med. & Surg. Monograph **5**:57, 1890. Wenckebach, K.: Arrhythmia of the Heart, London, W. Green and Son, 1904. Galli, G.: Contributo al Significato Pronostico delle Extrasystole Cardiache, Policlinico **25**: (sez. prat.) 1256, 1918. Smith, A. L.: Clinical Study of One Hundred Patients with Extrasystoles as Seen in Office Practice, Ann. Clin. Med. **3**:385, 1924. Mackenzie (footnote 3).

14. Bass, M. H.: Significance of Cardiac Extrasystoles in Childhood, J. A. M. A. **86**:387 (Feb. 6) 1926.

15. Lewis, T.: Clinical Disorders of the Heart Beat, London, Shaw & Sons, 1913.

16. Babcock, R. H.: Prognosis in Cardiac Affections, as Related to the Discovery of Murmurs and to Arrhythmia, J. A. M. A. **70**:355 (Feb. 9) 1918.

17. Reilly, T. F.: The Problem of the Irregular Heart, Internat. Clin. **4**:62, 1915.

their presence in organic heart disease increases the seriousness of the prognosis by 10 per cent. Vaquez,[18] Leconte[19] and Ritchie[20] looked on ventricular as less serious than auricular and nodal premature beats, and further considered their onset in hypertensive cases as the precursor or first sign of cardiac involvement.

Satterthwaite[21] considered premature beats in high temperatures as indicative of severe toxemia; in convalescence, of a weak heart; in pneumonia or rheumatic fever, as suggesting cardiac complications. Hewlett[22] quoted Mackenzie as saying that they are particularly ominous when they occur at the height of infectious fevers. Strickland-Goodall,[23] Smith[24] and Hirschfelder[25] emphasized the point that in a patient in whom premature beats are developed or increased by exercise, the prognosis is more serious. Nefedoff[26] looked on their presence in heart disease as enhancing the seriousness of the prognosis and he also believed them dangerous with high blood pressure, because cerebral hemorrhage may follow the large postextrasystolic beat. Roth[27] stated that nervous influences increase, but that it is doubtful if they can ever induce premature beats in an otherwise healthy organ. He mentioned focal infections as a cause of them and believed it more likely that the nervous influence merely augments the disturbance in a heart that is already the seat of some pathologic process or one that bears the brunt of at least a mild toxemia. Mortensen,[28] in speaking of premature beats, concluded that even though such causes as tobacco, tea and coffee are a factor in producing them, nevertheless, in the great majority of cases there is underlying cardiac disease, and all of the cases in which

18. Vaquez, H.: Prognostic et traitment des arrhythmies, Arch. d. mal. du couer **4**:3, 1911.

19. Leconte, M.: L'extrasystole, Paris, J. B. Baillière et fils, 1911.

20. Ritchie, W. T.: Prognosis in Certain Affections of the Heart, Lancet **2**: 643, 1920.

21. Satterthwaite, T. E.: Newer Conception of Cardiac Arrhythmias and Treatment, M. Rec. **75**:833, 1909.

22. Hewlett, A. W.: Common Cardiac Arrhythmias and Their Clinical Significance, Internat. Clin. **4**:47, 1907.

23. Strickland-Goodall, J.: The Premature Contraction and Its Significance, New York M. J. **115**:204, 1922.

24. Smith, F. M.: The Premature Contraction, Wisconsin M. J. **20**:114, 1921-1922.

25. Hirschfelder, A. D.: Diseases of the Heart and Aorta, Philadelphia, J. B. Lippincott Company, 1918.

26. Nefedoff, V.: Frequence, origine et signification des phenomenes extrasystoliques au coeurs des cardiopathies, Arch. d. mal. du coeur **6**:711, 1913.

27. Roth, I. R.: Cardiac Arrhythmias, New York, Paul B. Hoeber, 1928.

28. Mortensen, M. A.: Diagnosis and Management of Extrasystolic Type of Cardiac Irregularities, Lancet-Clinic **113**:353, 1915.

they appear must be looked on as potentially pathologic. Müller [29] voiced the most pessimistic opinion of all, affirming that, "There is no doubt extrasystoles in the majority of cases are due to incipient or advanced diseases of the myocardium. If a great number of extrasystoles disturb the normal pulse rate, we are always sure of a severe damage to the heart muscle. It is better in practice to consider them as signs of importance and not simply as the manifestation of a nervous heart which commonly passes as harmless."

Koppang [5] reported the results of 1,000 tracings taken in 62 cases following diphtheria. Forty-two of these patients had serious cardiac complications. In seventeen tracings he found premature contractions. They were present in the same frequency at varying rates and appeared from the tenth to the sixtieth day of convalescence, with two exceptions which occurred in patients with other cardiac complications. He concluded that premature contractions are a symptom of myocardial involvement following diphtheria in contrast to those encountered in routine practice. He also found them in 7 per cent of 200 cases of hypertension, but doubted if they were caused by high blood pressure. He had seen them frequently in patients with low blood pressure, and had also noted in cases of hypertension that they could be produced by psychic influences.

PRESENT STUDY

The lack of definite data as to the significance of premature beats at varying heart rates and the variable opinions expressed caused us to make the study herein reported. Are cases in which premature beats occur at the more rapid rates more serious than those in which they occur at the slower rates?

Our series is composed of 200 patients, 100 of whom showed premature beats and 100 normal rhythm. None of them evidenced a marked degree of auriculoventricular or intraventricular block. They were all seen and electrocardiograms were made at the Massachusetts General Hospital, between the years 1915 and 1926, and all have been followed to the present time. The clinical diagnoses in the cases of the two groups were similar. We have divided each group of 100 into four subgroups of 25 each, one with heart rates less than 80, one with rates between 80 and 100, one with rates between 100 and 120 and one with rates over 120.

Of the 100 patients who presented premature beats, 56 were males and 44 females. When they were grouped in the several decades according to their age at the time of examination, it was found that 5 were in the first decade, 9 in the second, 5 in the third, 10 in the fourth, 21 in

29. Müller, F.: Nervous Affections of the Heart, Arch. Int. Med. **1**:1 (Jan.) 1908.

the fifth, 27 in the sixth, 15 in the seventh, 7 in the eighth and 1 in the ninth. The incidence of cardiac disease, of disease elsewhere in the body and of the apparently healthy is shown in the accompanying table, in which our figures are compared with similar ones of Lewis and Pardee.[30]

The higher incidence among the healthy in our series may be due to the inclusion of more cases seen in private practice. Undoubtedly, premature beats among healthy persons at large are relatively much more frequent than the figures in the table indicate, as these series were, for the most part, collected from hospital cases.

The number of patients with premature beats who died in the different heart rate groups, together with the number of patients used as control cases who are dead, in each group, is shown graphically in chart 1. It will be seen that there is practically no increase in the death rate of the premature beat series until the heart rate of 120 is reached, and beyond that rate there is only a moderate increase. The

Incidence of Cardiac Disease, Disease Elsewhere in the Body and the Apparently Healthy

	Heart Disease, per Cent	Disease Elsewhere, per Cent	Healthy, per Cent
Lewis	71	19	10
Pardee	84	10	6
Present series	63	22	15

rather marked increase in the deaths of those of the control group with heart rates of from 100 to 120 we believe should probably be attributed to an insufficient number of cases in the series, as the clinical diagnoses in this group correspond closely to the diagnoses in the premature beat group. This inconsistency can be corrected partially by dividing each series into two groups, one with heart rates less than 100 and one with rates over 100. The graphic representation of the number of deaths when the two series are thus divided is shown in chart 2. It is seen then that the number of deaths in the two series correspond closely, and those cases in the premature beat series show a mortality at faster heart rates that is no higher than those of the control series with no premature beats. In other words, as the basic heart rate increases so does the mortality increase but no faster in those patients with premature beats than in those without premature beats.

Barker [31] reported a series of 193 patients with premature beats divided into one group of 76 who had no other signs of heart disease

30. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, 1928.

31. Barker, P. S.: Significance of Extrasystoles, Ann. Clin. Med. **2**:371, 1923-1924.

and a second group of 117 patients with premature beats with other signs of heart disease. In the former group the known dead with auricular premature beats amounted to 22.5 per cent, with ventricular premature beats, 17 per cent. In the latter the known dead among the auricular group was 51 per cent, among the ventricular, 27 per cent. Rearranging his cases we find that these two groups taken together

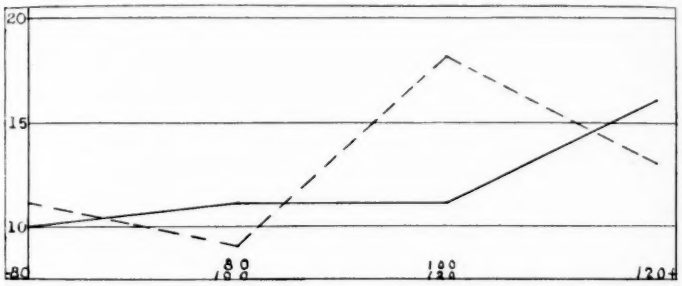

Chart 1.—The number of patients with premature beats who died, and the number of patients used as controls who died. The abscissae represent the number of patients dead, the ordinates the heart rates. The cases of premature beats are shown by the heavy line and the control cases by the broken line.

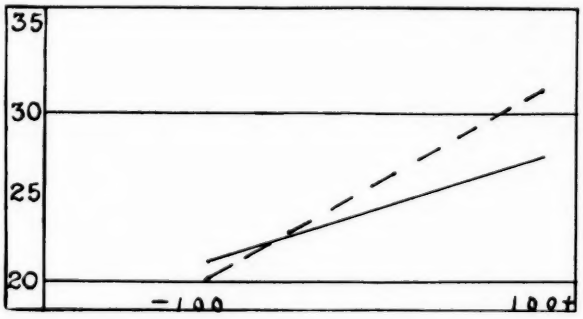

Chart 2.—The number of deaths in the series in which the heart rates were less than 100, and those in the series in which the heart rates were more than 100. The abscissae represent the number of patients dead, the ordinates the heart rates. The cases of premature beats are shown by the heavy line, and the control cases by the broken line.

show a total mortality for auricular premature beats of 36 per cent and a total mortality for ventricular premature beats of 27 per cent. In our series, we have followed all the cases and consequently have a higher mortality in both types; however, we find that the comparative

number of deaths among those of the auricular type (thirty-seven cases) and those of the ventricular type (sixty-three cases) is the same, the ventricular being slightly in excess. Our percentages show 45 per cent of the patients with auricular and 50 per cent of the patients with ventricular premature beat to be dead within a period of thirteen years.

In our group of cases we have 63 with ventricular premature beats. Of these, 55 were unifocal in origin and 8 were of multifocal origin. D'Irsay [32] studied 100 cases of premature beats, presumably ventricular, to determine the relative significance of those arising from multiple foci as compared with those arising from a single focus. He concluded that diseases representing pathologic change in the myocardium show a higher percentage of ventricular premature beats from multiple foci than from one focus. Forty-one of our patients with ventricular premature beats showed evidence of heart disease. Of these, 34, or 83 per cent, were unifocal and 7, or 17 per cent, were multifocal in origin. D'Irsay also stated that diseases not involving the heart are not accompanied by multifocal premature beats. In one of our cases multifocal premature beats were recorded without clinical or electrocardiographic evidence of any other abnormalities in the heart or elsewhere. This patient is living and well four years after the original electrocardiogram was taken. Furthermore, d'Irsay stated that the multifocal type gives a much more grave prognosis than the unifocal. In our series, among the patients who showed multifocal premature beats the mortality is 63 per cent as compared with 46 per cent mortality among those of the unifocal group. Many more cases must be studied before definite conclusions can be reached as to how much more serious multifocal extrasystoles may be than unifocal extrasystoles.

SUMMARY

1. A series of 100 cases of premature beats, divided into four heart rate groups, and followed over a period of years, is presented. This is accompanied by a series of a similar size of control cases, having the same diagnoses as those of the premature beat group but not showing arrhythmia.

2. Premature beats which occurred at the more rapid rates in this series did not bear a more serious prognosis than those at slower rates when allowance was made for the increase in mortality due to increased rate alone.

3. The presence of premature beats in the series reported here added no gravity to the prognosis. The death rate was actually slightly greater in the 100 cases with normal rhythm.

32. d'Irsay, S.: On the Meaning of Extrasystoles, Am. J. M. Sc. **174**:96, 1927.

4. Auricular premature beats were not found to be more significant so far as prognosis of life is concerned than were ventricular premature beats.

5. Multifocal ventricular premature beats did not appear to bear a much more serious prognosis than those of unifocal origin; neither were they present in our patients who showed evidence of heart disease to nearly the degree of those of the unifocal type. It is doubtful if multifocal premature beats are always accompanied by myocardial involvement.

6. The frequency with which premature beats occurred in a given case seemed to bear little relation to prognosis.[33]

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33. In our experience, the rare exceptions in which premature beats occur more often than once every other beat, tend to have auricular fibrillation or ventricular paroxysmal tachycardia and serious heart disease. Only four such cases, however, have been observed at the Massachusetts General Hospital in thirteen years in more than 5,000 cases in which electrocardiography was done. Also, it may be added that some years ago one of us reported a higher death rate in patients with auricular fibrillation when there was a complication of ectopic ventricular contractions. (White, P. D.: Prognosis in Heart Disease in Relation to Auricular Fibrillation and Alternation of the Pulse, Am. J. M. Sc. **157**:5, 1919.)

CHLORIDE METABOLISM AND ALKALOSIS IN ALKALI TREATMENT OF PEPTIC ULCER *

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Only within the last three years has the literature definitely suggested the important relation of chloride metabolism to alkalosis in the Sippy [1] alkali treatment for peptic ulcer. Hardt and Rivers [2] were probably the first to suggest that the symptomatology of alkalosis might be partly due to the reduction of blood chlorides; however, the chlorides were normal in the one case they examined. Work has been done on upper intestinal and pyloric obstruction [3] and on salt-poor [4] and salt-free [5] diets, but I have found no articles which compare the observations and symptoms of these conditions with the strikingly similar pictures found in alkalosis from Sippy treatment.

A study of the material in this paper and a comparison with the observations of others will show the paramount importance of chloride metabolism in the treatment for ulcers. I hope that a clearer understanding of the complications of Sippy therapy will result from studies such as these and help to quiet the dissatisfaction revealed in the literature. The objections of Smithies [6] are characteristic; however, the rapid symptomatic relief, the high percentage (about 85 per cent) of conditions cleared up symptomatically and roentgenologically, and even the rapid clearing of partial pyloric obstruction [1] from spasm and edema are results not readily obtained with other methods of therapy.

SIGNS AND SYMPTOMS AND RESULTS OF LABORATORY EXAMINATION IN ALKALOSIS

With a clear picture of the alkalosis from alkali therapy in mind, one can make comparisons with the alkalosis of chloride depletion and of chloride privation. Then one can see more clearly the relationship and importance of chloride metabolism to alkali treatment.

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1. Sippy, B. W.: Gastric and Duodenal Ulcer, J. A. M. A. **64**:1625 (May 15) 1915; ibid. **79**:26 (July 1) 1922.

2. Hardt, L. L., and Rivers, A. B.: Toxic Effects of Alkali Treatment, Arch. Int. Med. **31**:171 (Feb.) 1923.

3. Haden, R. L., and Orr, T. G.: Acute Symptoms Following Gastroenterostomy, Bull. Johns Hopkins Hosp. **34**:26, 1923; Blood Changes After Intestinal Obstruction, Surg. Gynec. Obst. **37**:465, 1923. MacCallum et al: Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins Hosp. **31**:1, 1920.

4. Austin, J. H., and Jonas, L.: Effect of Diet on Chloride Excretion in the Dog, J. Biol. Chem. **33**:91, 1918. Mayer (footnote 24).

5. Frouin, A.: Chlorides and Gastric Secretion, Presse méd. **30**:1096, 1922.

6. Smithies, Frank: Non-Surgical Management of Peptic Ulcer, J. A. M. A. **85**:674 (Aug. 29) 1925.

Symptoms ascribed to alkalosis by various writers are lassitude, irritability, dizziness, distaste for food, nausea and vomiting, aching in the muscles and joints, slow respirations, increased pulse rate,[2] dry throat, dry and itching skin,[7] mental dulness and stupor, dull headaches and even muscular twitchings and tetany.[8]

In one case I observed a marked craving for salt, and in cases of chronic alkalosis, marked weakness, especially in the legs, fatiguability, dyspnea on exertion and cramps in the legs. A few patients have shown absolute intolerance to neutralizing doses of alkali; one patient developed marked nausea and vomiting even though there was considerable free acid in the gastric contents. Another patient developed diarrhea, apparently due to the soda in the powders.

In some cases, Hardt and Rivers [2] and Venables [9] reported evidence of disturbed kidney function with profound toxic symptoms and even death. Albumin, pus, erythrocytes and casts were found in the urine; the blood urea and plasma carbon dioxide capacity were increased, and the phenolsulphonphthalein output of the kidneys was depressed. MacCallum [10] has shown that the depletion of chlorides by vomiting and aspiration produces symptoms of alkalosis, nerve irritability and tetany in dogs. In addition, Hastings, Murray and Murray [11] noted a rise of carbon dioxide capacity. Frouin [5] noted lassitude, dulness, muscular twitching and weakness, paresis of the posterior extremities and convulsions with fits of anger in dogs kept on salt-free diets. Achlorhydria occurred on the eighth day, and after three weeks diminished secretion in the stomach, diminished absorption in the intestine and a diminution of all the mineral salts obtained. He said that Bischoff found a diminished excretion of urea. Houghton [12] and Haden and Orr [13] observed lassitude, dulness, evidence of uremia, tetany, etc., in the hypochloremia of pyloric and upper intestinal obstruction.

The carbon dioxide capacity of the plasma [14] has been used considerably as a measure of alkalosis. Kast, Myers and Schmitz [15] indi-

7. Jordan, S. M.: Calcium, Chlorides and Carbon Dioxide Content of Blood in Alkali Treatment, J. A. M. A. **87**:1906 (Dec. 4) 1926.

8. Grant, S. B.: Tetany: Report of Cases with Acid-Base Disturbance, Arch. Int. Med. **30**:355 (Sept.) 1922.

9. Venables, J. F.: Alkalosis Following Alkali Treatment, Guy's Hosp Rep. **75**:152, 1925.

10. MacCallum (footnote 3, third reference).

11. Hastings, A. B.; Murray, C. D., and Murray, H. A.: Changes in Blood After Pyloric Obstruction, J. Biol. Chem. **46**:223 1921.

12. Houghton, L. W.: Toxemia Following Pyloric Obstruction, Guy's Hosp. Rep. **75**:149, 1925.

13. Haden and Orr (footnote 3, first and second references).

14. Van Slyke, D. D.: Determination of Carbonates and Carbon Dioxide in Solutions, J. Biol. Chem. **30**:347, 1917.

15. Kast, L.; Myers, V. C., and Schmitz, H. W.: Alkalosis, J. A. M. A. **82**: 1858 (June 7) 1924.

cated that the p_H as well as the carbon dioxide content should be taken to get a true picture of the acid-base balance. The carbon dioxide content is said to give more information than the capacity, because, according to van Slyke,[16] the p_H is a function of the ratio of basic carbonates to carbonic acid ($BHCO_3$: H_2CO_3 ratio), an increase in the ratio increasing the p_H; the carbon dioxide content is the sum of carbon dioxide as carbonic acid and carbonates. In the average case of alkalosis from alkali therapy, however, there is little consistent difference. Myers and Gatewood[17] found this to be true.

Myers and Booher[18] and van Slyke[19] showed that the carbon dioxide capacity or content is not necessarily increased in alkalosis, and, on the other hand, increased carbon dioxide capacity does not always indicate true alkalosis, as the p_H may be normal. A p_H above 7.47 indicates a true uncompensated alkalosis. Unfortunately, I could make few p_H determinations simultaneously with the determinations of the carbon dioxide content and capacity.

OTHER EFFECTS OF ALKALI

After a course of alkali therapy, Friedenwald[20] found in 44 per cent of his cases an increased free and total acid, in 22 per cent a diminished secretion and the rest were irregularly affected. Lockwood and Chamberlin[21] gave alkali with the test meal. There was a temporary neutralization, but afterward a tendency for the acid secretion to rise above normal in 50 per cent of the patients given sodium bicarbonate, in 25 per cent of those given calcium carbonate and in 20 per cent of those given magnesium oxide. The temporary neutralizing effects of the last two alkalis were more prolonged.

I obtained the gastric response from day to day while the patient was on alkali therapy, but in the two cases studied longest, large frequent aspirations on account of partial pyloric obstruction depleted the chloride reserve. Low chloride reserve diminishes acid secretion.[5] Therefore, these results are inconclusive as to the effect of alkalis per se on gastric secretion.

The observations of Friedenwald and of Lockwood and Chamberlin have formed the basis of one of the strong objections to alkali therapy;

16. Van Slyke, D. D.: Studies in Acidosis, J. Biol. Chem. **30**:289, 1917.

17. Myers and Gatewood: Acid-Base Balance in the Blood of Peptic Ulcer Cases Treated with Alkalies, Paper at the annual meeting of the American Gastro-Enterological Association, Atlantic City, N. J., May 2, 1927.

18. Myers, V. C., and Booher, L. E.: Variations in Acid-Base Balance of the Blood in Disease, J. Biol. Chem. **59**:699, 1924.

19. Van Slyke, D. D.: Variations of Acid-Base Balance of the Blood, J. Biol. Chem. **48**:153, 1921.

20. Friedenwald, J.; Gantt, W. H., and Morrison, T. H.: Studies in Fractional Analysis, Ann. Clin. Med. **2**:292, 1924.

21. Lockwood, A. L., and Chamberlin, H. G.: Effects of Alkali on Gastric Secretion and Motility, Arch. Int. Med. **32**:74 (July) 1923.

however, an increase of acid secretion, which is likely a temporary affair, will not be a serious drawback if the neutralization of free acid is obtained without producing other complications. I have not found studies definitely indicating more frequent recurrence of ulcer after treatment with alkali.

In the blood of patients under alkali treatment, Sara M. Jordan [7] found some increase of calcium, depression of chlorides, most marked in the first few days and then settling to a level, and elevation of carbon dioxide content. In addition, Myers and Gatewood [17] studied the p_H, the nitrogenous products and other constituents of the blood which might play a part in producing symptoms of alkalosis.

I have followed the general chloride metabolism as closely as possible to determine the rôle played by variations in the chloride balance. A test meal of 50 cc. of 1 per cent cooked corn starch, containing 1 cc. of 0.5 per cent phenolphthalein and neutralized until barely pink with tenth normal sulphuric acid, was introduced into the stomach while fasting, through a Rehfuss tube after complete aspiration. After half an hour the gastric contents were withdrawn and a sample of oxalated blood was obtained. The blood was kept from contact with air by the use of liquid petrolatum.

REPORT OF CASES

As an introduction to the discussion, excerpts from a few random case histories will be given and some partial observations tabulated.

Acute Hypochloremia with Normal Carbon Dioxide Capacity.—CASE 1.—E. G., a white man, aged 26, had a condition that was diagnosed duodenal ulcer and irritable colon. The urine showed a faint trace of albumin with sulphosalicylic acid. The blood showed nonprotein nitrogen, 31.3 mg. per hundred cubic centimeters (normal from 25 to 35). The kidney function was 50 per cent phenolsulphonphthalein output in two hours (normal from about 50 to 70 per cent). Sippy treatment was started on March 8, 1926, with 55 soda units (40 grains [2.6 Gm.] of powder containing three parts soda and one part calcium carbonate). On March 10, the aspirations were acid. On March 11, the milk "tasted bad," nausea and a dull feeling in the head developed and the patient craved something salty. To date, the aspirations totaled 315 cc., representing about 1.5 Gm. of sodium chloride. (For convenience, all chlorides are expressed as sodium chloride.) The whole blood chlorides were 410 mg. per hundred cubic centimeters (normal about 450), and the plasma chlorides were 500 (normal about 570). The carbon dioxide capacity of the plasma was 65 per cent by volume (normal from 55 to 65). The treatment with alkali was discontinued for two days, and then the patient was given 43 units (30 grains [1.95 Gm.]) per dose.

On March 14, he complained of crampy abdominal pain with gas and said the bowels felt as though they were "burning up." That night there were several watery brown stools. He complained of these symptoms more or less until he left the hospital. Enemas of physiologic solution of sodium chloride and phenolated solution of iodine gave some relief. On March 16, he was again given 55 units of alkali, because the aspirations remained acid practically all the time. The dosage of powder was increased to 65 units on March 19. On the next day, the carbon dioxide capacity was 65.9 and the blood chlorides 440. Aspirations to date totaled

1,150 cc., representing about 6 Gm. of sodium chloride. There were no symptoms to suggest alkalosis. On March 21, supplementary feedings were started and he tolerated the 65 units without difficulty.

CASE 2.—S. B., a white man, aged 30, had a condition that was diagnosed duodenal ulcer and irritable colon. The urine contained a slight amount of albumin on one occasion. The blood showed nonprotein nitrogen, 34.1; urea nitrogen, 16.3 (normal from about 12 to 15). Sippy treatment was started on Nov. 5, 1925, with 55 units of alkali. On November 7, the dosage of alkali was increased to 80 units. On November 8, the patient complained of a "shaky sensation," nausea and headache, and began to vomit. Aspirations had totaled only about 0.25 Gm. of sodium chloride. The dose of alkali was reduced to 55 units, but he was still nauseated on November 9. The carbon dioxide capacity was only 63.5, so he was given 80 units per hour between 11:30 a. m. and 6:30 p. m. Headache, nausea, vomiting and weakness continued. Finally, on November 11, he was put on a bland diet with three feedings per day and 83 units of alkali an hour after meals and at bedtime. Two weeks later he reported that the symptoms of ulcer were gone, but he had a burning sensation in the epigastrium. The diagnostic fractional test meal had shown a free acid of from 72 to 116 units. The alkali may have further increased the acid secretion[23] after the period of temporary neutralization and caused burning distress. The powder was increased to six doses per day.

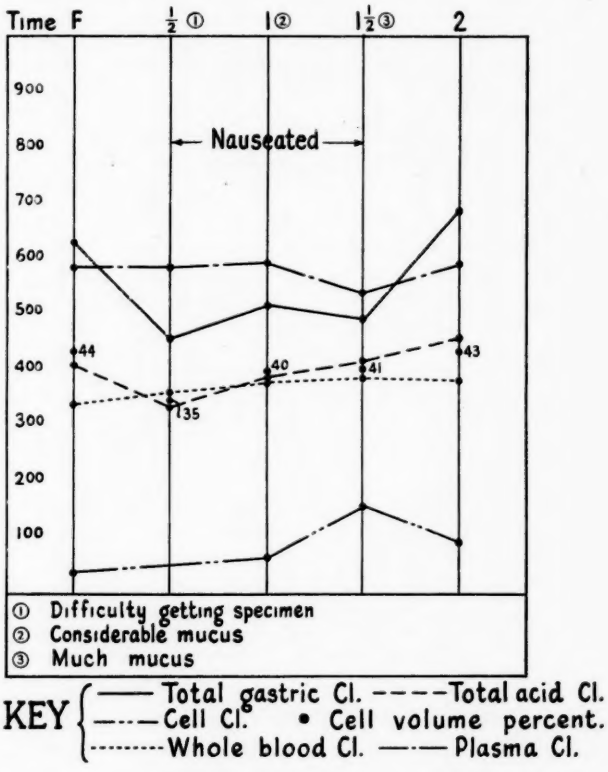
On Sept. 16, 1926, he returned with recurrent ulcer distress. He vomited that night. The next day the plasma chlorides were 570 and the carbon dioxide capacity 64.7; he was started on Sippy therapy with 55 soda units. The next day he had a headache and was irritable. The carbon dioxide capacity was 66.6. Because all aspirations were acid, the alkali was increased to 80 units on September 20. The urine was normal. The next day he felt that the cream did not "agree" with him. Whole milk was substituted for the mixture of equal parts of milk and cream. In twenty-four hours, the blood chlorides had dropped from 430 to 360 and the carbon dioxide had risen from 61.7 to 68.4. There was increasing nausea. By 4 p. m., the carbon dioxide capacity was 70.3, but the blood chlorides were reported as 390. The urea was 13.5. The intravenous injection of 500 cc. of 5 per cent solution of sodium chloride cleared up the general feeling of heaviness, the distaste for food and other symptoms of alkalosis within five minutes, but he complained of excessive thirst, tightness in the chest and had chilly sensations for an hour. He then felt all right and began to take the powders and milk. The blood chlorides were now 460 and the carbon dioxide 66.6. The range of the temperature remained normal. Hourly samples of urine, from 5 to 9 p. m., showed the excretion of urea to be 2.6, 1.9, 0.87, 0.69 and 0.62 Gm.; the excretion of chloride, 1.18, 1.62, 1.12, 0.42 and 0.41 Gm., consecutively. The phenolsulphonphthalein output of the kidneys was 60 per cent for two hours. At 9 p. m., the blood chlorides were 380, but the next day they increased to 420, with a carbon dioxide capacity of 62.7.

Because of the marked intolerance to alkali therapy, a gastro-enterostomy was done.

The accompanying chart shows the observations in a case of chronic hypochloremia. The blood chlorides were from about 15 to 20 per cent below normal, and had probably been subnormal to that degree for some time, in view of the symptoms of drowsiness, nausea, headache and weakness. The patient received Sippy treatment over a period of two years. He consulted me only for diagnosis.

Table 1, case 3, shows the record on a case of acute hypochloremia apparently resulting partly from chloride depletion and precipitated and aggravated by alkali.

CASE 3.—J. B., a man, aged 48, a foreman in a forge shop, had a condition of fifteen years' duration that was diagnosed ulcer, with a 75 per cent retention after six hours. He weighed 110 pounds (49.9 Kg.), the ideal weight being 148 pounds (67 Kg.). He had taken sodium bicarbonate for the relief of the condition. The kidney function was: phenolsulphonphthalein return, 43 per cent in two hours. The urine showed a gravity of 1.012, without albumin. The blood showed hemoglobin, 109 per cent, and red blood cells, 4,550,000.



J. T., aged 23, had a condition that was diagnosed irritable colon and duodenal ulcer (healed) of seven years' duration. The patient was examined on Jan. 26, 1926. In the chart all chlorides are expressed in the equivalent of sodium chloride in milligrams per hundred cubic centimeters.

Alkalosis with Calcium Carbonate.—CASE 4.—R. M., a man, had a condition diagnosed duodenal ulcer and irritable colon. Ulcer therapy was started on May 17, with calcium carbonate, 20 grains (1.3 Gm.) per dose. On May 20, the blood chlorides were 420 and the carbon dioxide capacity 66.6. The dosage of calcium carbonate was increased to 30 grains (1.95 Gm.) per dose, because the free acidity was not neutralized. On May 21, the blood chlorides were 410, the carbon dioxide

capacity, 79.1; headache, nausea and lassitude, symptoms of alkalosis, obtained. To that date, aspirations from the stomach were small and there was no diarrhea to deplete the reserve of chloride.

Alkalosis with Sippy Powders.—Case 5.—B. B., a man, had a condition that was diagnosed duodenal ulcer. Sippy therapy was started on Feb. 27, 1927, with 55 units. On March 1, he had an uneasy feeling in the stomach and a dull headache. The next day, the headache disappeared, but the uneasy feeling in the stomach continued. The blood chlorides were 390, the carbon dioxide capacity, 83.8. Alkalis were discontinued, and on March 3 the carbon dioxide capacity was 68.4.

In table 2, case 6, the cause of the alkalosis is not clear. Other factors complicated the picture. This case was carefully studied.

Case 6.—O. M., a man, aged 48, a foreman in a lumber yard, had a condition diagnosed duodenal ulcer, with a retention of 100 cc. at 11 p. m.; he had also a deformed appendix, secondary syphilis and chronic tonsillitis. He had taken sodium bicarbonate for relief from pain. The test for kidney function showed a phenolsulphonphthalein return of 70 per cent in two hours. On May 19, 1927, the urine had a gravity of 1.006, without albumin; on May 27, the gravity was 1.016, without albumin. On May 25, the blood showed 85 per cent hemoglobin; on May 30, 95 per cent hemoglobin and 4,250,000 red blood cells.

Compensated Alkalosis.—Case 7.—R. T., a woman, had a condition that was diagnosed duodenal ulcer with partial pyloric obstruction. Sippy therapy was started on Jan. 14, 1927. The carbon dioxide capacity was 61.4; the blood chlorides, 445, and the urea, 12.1. On January 17, the carbon dioxide was 73 and the chlorides 470; on January 22, 71.9 and 440, respectively. The dosage of powder was then reduced to 40 units, and supplementary feedings were started. Apparently, aspirations had not been large enough to deplete the chloride reserve sufficiently to produce hypochloremia, and the alkalis caused no apparent disturbance of chloride metabolism. Not until after a week of therapy did the patient show definite improvement of the pyloric obstruction. On January 21, the aspiration at 11 p. m. yielded 180 cc.; on January 24, 65 cc., and on the next day, 30 cc. No symptoms of alkalosis developed with the increase of carbon dioxide capacity. Therefore, apparently there was compensation throughout the course of treatment at the hospital.

In the following case, I do not understand the low carbon dioxide readings. A check determination by the central laboratory on June 14 gave a result similar to mine. My personal observations in this case, aside from the results tabulated, were negligible. The blood sugar was 74 mg. per hundred cubic centimeters (normal from about 80 to 85). The urine showed no albumin or sugar on several examinations; no tests were made for acetone bodies. Diabetes would complicate the relationship of the chlorides to the other observations, since the blood of diabetic patients has a low chloride content.[23] An inanition acidosis might account for the low readings—the patient lost 6 pounds (2.7 Kg.) in the week before treatment was started. There was no pyloric obstruction.

22. Host, H. F.: Chloride Metabolism, J. Lab. & Clin. Med. **5**:713, 1919-1920.

23. Eisenman, A. J.; Bulger, H. A., and Peters, J. P.: Acid-Base Equilibrium Studies, J. Biol. Chem. **67**:219, 1926.

TABLE 1.—*Observations in Case 3*

Date, 8 a.m.	Blood: Cell Volume	Blood: Chloride as Mg. of Sodium Chloride per 100 Cc.: Blood	Plasma	Cell	Nonprotein Nitrogen and Urea	Carbon Dioxide Capacity	Gastric Contents: Phenolphthalein, per Cent	Volume Test Content	Hydrochloric Acid: Free Units	Total Units	Total as Sodium Chloride	Total Chloride as Sodium Chloride	Twenty-Four Hour Chlorides in Grams: Output: Urine	Stool	Aspirations* (Estimated Sodium Chloride Equivalent)	Intake: Diet	Intravenous Sodium Chloride	Chloride Balance	Remarks
5/17	0.50?	453	444	336?	29.4	59	25	100	32	44	257	540	....	....	0.75 (150 cc.)	....	...	....	Admitted to hospital
5/18	0.365?	444	527	269?	33.3 15.0	..	33	75	35	43	252	452	6.86	....	8.13 (1,625 cc.) vomitus ? cc.	2.0	...	—13+	Tincture of belladonna, 20 m. three times a day; phenobarbital, 0.5 grains three times a day; nausea and vomiting during night; milk and cream, 4 ounces every quarter hour from 9 a. m. to 6 p. m.
5/19	0.42	490	581	364	....	..	20	70	32	40	234	571	1.10	0.32	9.0 (1,800 cc.)	2.24	...	— 8.2	Fairly comfortable; calcium carbonate, 16 doses of 20 grains each
5/20	0.42	459?	545?	340?	....	62	30	40	55	62	393	480	0.31	0.06	3.18 (635 cc.)	2.24	...	— 1.3	Slight nausea; calcium carbonate, 17 doses of 30 grains each
5/21	0.40	324	416	186	....	61	17	70	23	30	176	488	0.05	0.05	4.73 (945 cc.)	2.24	...	— 2.6	Nausea and vomiting all night; lassitude, headache, nervousness
5/22	0.38	354	449	200	50.0 33.4	66	2.5?	35	12.5	18.7	109	577	0.14	0.55	0.45 (90 cc.)	0.20	2.5	+ 1.6	Feels better; doses of calcium carbonate discontinued
5/23	....	320	...	...	49.2 29.4	..	..	..	..	..	...	...	....	....	.....	....	2.5	.....	
5/23 (4 p.m.) 5/24 (8 a.m.)	460 320	...	...	....	53	..	..	..	..	...	...	....	....	.....	....	16.0	.....	Sodium chloride given in divided doses between 8 a.m. and 4 p.m.	
		Gastro-enterostomy done on 5/25/27																	

* One hundred cubic centimeters of average contents was estimated to be equivalent to 0.5 Gm. of sodium chloride.

TABLE 2.—*Observations in Case 6*

Date, 8 a.m.	Blood: Cell Volume	Blood: Chloride as Mg. of Sodium Chloride per 100 Cc.: Blood	Blood: Chloride as Mg. of Sodium Chloride per 100 Cc.: Plasma	Blood: Chloride as Mg. of Sodium Chloride per 100 Cc.: Cell	Blood: Nonprotein Nitrogen and Urea	Blood: Carbon Dioxide Capacity	Gastric Contents: Phenolphthalein, per Cent	Gastric Contents: Volume Test Content	Gastric Contents: Hydrochloric Acid: Free Units	Gastric Contents: Hydrochloric Acid: Total Units	Gastric Contents: Hydrochloric Acid: Total as Sodium Chloride	Gastric Contents: Total Chloride as Sodium Chloride	Twenty-Four Hour Chlorides in Grams: Output: Urine	Twenty-Four Hour Chlorides in Grams: Output: Stool	Twenty-Four Hour Chlorides in Grams: Output: Aspirations* (Estimated Sodium Chloride Equivalent)	Twenty-Four Hour Chlorides in Grams: Intake: Diet	Twenty-Four Hour Chlorides in Grams: Intake: Intravenous Sodium Chloride	Chloride Balance (Approximate)	Remarks
5/25	Sample lost	460	Lost sample		....	..	1.25	50	21F† 17½T	32F 23½T	187F 137T	503F 480T	....	....	0.75 (150 cc.)	....	...	.....	Admitted to hospital
5/26	0.36	431	555	211	.... 16.8	50	2.25	25	27F 27½T	38F 36T	222F 211T	540F 540T	3.61	....	2.48 (495 cc.)	2.5	...	— 3.0	Tincture of belladonna, 20 m. three times a day; milk and cream, 4 ounces every hour from 9 a.m. to 6 p.m.; no complaints
5/27	0.39	421	556	210	35.0 17.5	52	2.6	35	50F 40T	57F 48½T	333F 284T	588F 503T	2.35	....	4.13 (825 cc.)	2.5	...	— 4.0	No complaints; calcium carbonate, 16 doses of 30 grains each; phenobarbital, 0.25 grain four times a day
5/28	0.35	433	530	251	40.0 17.9	57	9.0	125	10F 38T	20F 45T	117F 263T	543F 510T	0.63	0.22	2.80 (560 cc.)	2.5	...	— 1.15	Nauseated; pain during night; calcium carbonate, 17 doses of 30 grains each
5/29	0.39	453	550	300	.... 15.8	52	6.7	125	29F 75T	43F 81T	252F 474T	686F 695T	1.19	....	1.70 (340 cc.)	5.8	...	+ 2.9	Feels "rotten"; pain; supplementary feedings started; lumbar puncture
5/30	0.34	465	529	341	.... 14.7	63	6.25	65	18½F 53½T	37F 64T	216F 374T	644F 615T	0.92	....	1.30 (260 cc.)	10.6	...	+ 8.4	Still feels "rotten"; drowsy, "funny" feeling in head relieved partially by lying down
5/31	....	...	...	...	....	..	.....	..	....	....	.....	.....	2.24	1.04	0.73 (145 cc.)	10.6	5.0	+11.6	No definite change; tonsillectomy done after examination

* One hundred cubic centimeters of average contents was estimated to be equivalent to 0.5 Gm. of sodium chloride.
† F denotes fasting contents; T, test contents.

CASE 8.—C. A., a man, aged 46, had a condition that was diagnosed duodenal ulcer (without evidence of retention). Treatment for ulcer was started at 4 p. m. on June 13, 1927, with calcium carbonate, 20 grains (1.3 Gm.) per dose. On June 15, the dose was increased to 30 grains (1.95 Gm.). No note was made of symptoms of alkalosis. The observations are shown in table 3.

TABLE 3.—*Observations in Case 8*

Date	Time	Blood Chloride	Plasma Chloride	Urine Chloride	Nonprotein Nitrogen	Urea Nitrogen	Carbon Dioxide Content	Carbon Dioxide Capacity	p_H
6/14/27	9 a.m.	440	...	...	35.7	14.9	....	44.5	....
6/15/27	4 p.m.	410	...	...	....	....	43.85	....	7.38
6/16/27	9 a.m.	402	525	224	66.6	21.7	49.8	55.0	7.56
6/18/27	9 a.m.	444	536	...	36.3	21.0	46.4	49.5	7.52

COMMENT

The study of these and other cases convinces me of the importance of chloride metabolism in a treatment for ulcers. The intake of chlorides by patients on the Sippy milk diet without supplementary feeding is low—about 2 Gm. instead of the optimum of 5 Gm. or so per day—although an intake of only 1.25 Gm. per day for several weeks has been tolerated.[24] Therefore, the Sippy milk diet probably supplies enough chlorides unless there is disturbance by the alkalis or depletion by vomiting, aspirations or diarrhea.[22] In spite of the success of Molnár and Csáki [25] in controlling cases of simple hyperacidity by the restriction of the chloride intake, I favor, if anything, the addition of small amounts of sodium chloride to the powders and milk of patients on the Sippy treatment to insure a positive balance until supplementary feedings are started. There must be a marked depression of chloride reserve before gastric secretion is affected. I believe from 5 to 10 Gm. of sodium chloride daily will serve as a prophylactic against depletion and disturbances of chloride balance by alkali. Ammonium or calcium chloride must not be used for reasons considered later.

Sodium chloride is of value in the treatment of some patients with alkalosis. It is of greatest benefit in cases like 1 and 2. Results are fair in patients with marked depletion (case 3), and sodium chloride is of no definite benefit to patients with little or no depression in the amount of blood chlorides (case 6).

In my cases of ulcer there seemed to be four types of alkalosis. In the uncompensated type were found: (1) those persons with normal plasma carbon dioxide capacity and a hypochloremia which results from

24. Mayer, A.: Observations on the Urine with Salt-Poor Diet, Compt. rend. Soc. de biol. **58**:377, 1905.

25. Molnár, B., and Csáki, L.: Hyperacidity as a Disturbance of Chloride Metabolism, Ztschr. f. klin. Med. **100**:239, 1924; abstr., J. A. M. A. **83**:77 (July 5) 1924.

the alkalis themselves (cases 1 and 2) or partly from the depletion of a pyloric obstruction (case 3); (2) those with high carbon dioxide capacity and hypochloremia (cases 4 and 5); (3) and possibly a type with no distinct change of carbon dioxide or chloride content (case 6—only one case like this). (4) The compensated type has no symptoms referable to alkalosis, and the carbon dioxide content is high with normal amounts of chlorides (case 7). The patients with chronic alkalosis have a normal carbon dioxide content and hypochloremia (chart 1). The patient with a chronic case with adequate quantities of chlorides in the supplementary feedings would probably not be benefited by further additions of sodium chloride. In the uncompensated type, the intravenous injection of physiologic solution of sodium chloride gives prompt results; however, care must be taken not to give doses too large, too frequently or in too concentrated a form, lest excessive thirst, tightness in the chest, contraction and burning of the throat and chilly sensations or pyrexia, symptoms of acute hyperchloremia, set in (case 2). The total amount required may be gaged somewhat by the estimated chloride deficit (tables 1 and 2). A secondary fall of blood chlorides several hours after an injection may be expected, and sodium chloride should be given until the symptoms of alkalosis have disappeared or a normal equilibrium of blood chlorides is reached. Care must be taken not to go too far beyond this point, lest disturbed kidney function, edema, nausea and vomiting, marked sinus bradycardia and lowered blood pressure, signs of "chronic" hyperchloremia, set in.

In the laboratory diagnosis of alkalosis, the plasma carbon dioxide capacity [14] is not a criterion of alkalosis, neither is the carbon dioxide content.[26] The former is normally a little bit higher. Both are elevated in some types of alkalosis (cases 4 and 5), with a proportionally greater difference in the greater degrees of alkalosis (case 8). In patients with symptoms of alkalosis, I found, with one exception (case 6), an unusual depletion of blood chlorides, especially in the cells (chart 1). In the case not following this rule, I believe a simultaneous determination of carbon dioxide content and capacity would have revealed a difference greater than normal, thus suggesting an increased ratio of basic carbonates to carbonic acid, which in turn indicates an increased p_H, the true measure of alkalosis. Accurate p_H determinations [27] are difficult to make unless one is doing a number of them regularly. In compensated cases with high carbon dioxide readings, one might find a normal difference between the capacity and content.

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26. Van Slyke, D. D., and Neill, J. M.: Determination of Gas in Blood by Vacuum Extraction and Manometric Measurement. J. Biol. Chem. **61**:523, 1924.

27. Hastings, A. B., and Sendroy, J.: Colorimetric Determination of p_H without Buffer Standards, J. Biol. Chem. **61**:695, 1924. Cullen, G. E., and Biilmann, E.: Quinhydrone Electrode for Hydrion Determination in Serum, J. Biol. Chem. **64**:727, 1925.

The capricious variations of blood chlorides following intravenous injections of sodium chloride indicate that one can tell nothing about the chloride reserve of the body by a simple analysis of the blood for chlorides. One can tell little more by following the chloride balance day after day. There is the suggestion of a shift in body chlorides caused by the alkalis (table 1), but where the storage places are is as puzzling as in the chloride retention of pneumonia [22] in which the chlorides are also low.[23] The skin may take up a large part of it.[28] The urine seems to be the most sensitive indicator of approaching alkalosis (the drop in the chloride of the urine should be noted in tables 1 and 2), but does not suggest the status of the chloride reserve or the blood chlorides. The amount excreted in the stools is negligible and suggests that calcium carbonate does not reduce the absorption of chloride.[29]

The odd change in the gastric response accompanying alkalosis is apparently due to the systemic action of alkali. In the case in table 1, I do not understand the rise and drop in free and total acid without an accompanying change in the total gastric chlorides. There is a similar rise and drop in the acid of the contents of the stomach while fasting in the case reported in table 2, but in the test contents the acid rises with a slight drop on May 28 and a greater drop on May 30. In studying the acid secretion of several patients with ulcers, I thought I could detect, in the routine aspiration at 4 p. m., 9 p. m. and 11 p. m. (in patients with retention), a tendency of the acid secretion to rise the day before the symptoms of alkalosis occurred. This was particularly true of the aspiration at 11 p. m., which may be taken to represent the contents of the stomach while fasting. When alkalosis occurred, the acid secretion was much reduced. These changes were not constant or definite enough to be of value in detecting the tolerance point to alkali. Careful weighing of the evidence indicates that the local action of alkali, the local or systemic action of belladonna given to these patients and gastric fatigue played little, if any, part in the reduction of the acid secretion. In case 3, the depletion of chloride may have played a part and the alkalis precipitated and aggravated the condition.

A study of the dilution of phenolphthalein in the test meal [30] yielded no observations of definite value. Table 1 shows a slight rise in the percentage of phenolphthalein when nausea began and a fairly marked drop when the administration of alkali was discontinued because of alkalosis. Without characteristic changes in volume, these observations are

28. Sollman, Torald: A Manual of Pharmacology, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 777.

29. Goldschmidt, S., and Bingers, C. A. L.: Effect of Calcium on Intestinal Absorption of Sodium Chloride, Am. J. Physiol. **48**:473, 1919.

30. Gorham, F. D.: Factor of Dilution in Gastric Analysis, J. A. M. A **41**: 1738 (Nov. 24) 1923.

difficult to interpret. The increased percentage with the onset of nausea might indicate a slower emptying of the stomach. This suggests also a decrease of the volume of secretion, as the volume of contents is about the same or lower. The fairly low percentage and drop of volume when the doses of alkali were discontinued may mean that the pyloric obstruction was beginning to yield to treatment. In case 6, a rise occurred when alkalosis appeared; however, with the presence of epigastric pain, it was thought that the ulcer rather than the alkali might account for most of the symptoms, so the alkali therapy was not discontinued. Therefore, the percentage of phenolphthalein remained high. The increases in volume in the first two days of symptoms suggest that the delay of the emptying time was playing a large part in the result, but the third day the drop in volume hints that there was a decrease of secretion. It is preposterous to try to estimate the volume [31] of secretion in an aspiration made after an interval of half an hour, when one considers that on the last day the patient in case 3 would have secreted 1,920 cc. in the half hour interval, and the one in case 6, 3,950 cc. in that time on the first day.

The blood urea and nonprotein nitrogen seemed to increase only when there was a marked depletion or when the alkalosis was marked or prolonged. The intravenous injection of physiologic solution of sodium chloride increased the excretion of urea in case 2, but not much of the salt was poured out into the urine. Apparently, my cases were not profound enough to give evidence of kidney disturbance, and damaged kidneys played no part in precipitating the alkalosis.[9]

With a clear picture of the symptoms and observations in my cases, I shall now consider the problem of the pathogenesis of alkalosis. Whether there is chloride privation,[5] depletion [32] or depression by alkalis,[33] the symptoms are much the same. I therefore feel justified in ascribing much of the symptomatology to the hypochloremia which results. The unquestionable shift in balance between tissue and blood chlorides profoundly affects the nervous system, the vegetative portion of which seems to give the most positive signs of alkalosis. An upset in the balance between the sympathetic and the parasympathetic divisions can be made to explain many of the symptoms. I believe that in alkalosis there is a primary stimulation of the sympathetic system followed by a depression. To stimulation one may ascribe the warm,

31. Keefer, C. S., and Bloomfield, A. L.: Clinical Study of Gastric Function, J. A. M. A. **88**:707 (March 5) 1927.

32. Haden and Orr and MacCallum (footnote 3). Hastings, Murray and Murray (footnote 11). Houghton (footnote 12).

33. Hardt and Rivers (footnote 2). Jordan (footnote 7). Grant (footnote 8). Venables (footnote 9).

dry skin, the primary state of restlessness, nervousness, irritability, diarrhea, decreased respiration (which may be due to the increased capacity of the blood to carry carbon dioxide) and rapid pulse. The sympathicotonic person is said to have a tendency toward deficient acidity, a warm dry skin, a rapid pulse, is lively, excitable, has a rosy color, mobile dilated pupils, a fairly moist throat and a diminished or absent oculocardiac reflex. He is sensitive to epinephrine, pituitary extract and thyroid.[34]

In the more toxic state in alkalosis there are marked mental dulness and stupor, muscular twitchings, marked sweating, slow pulse and marked nausea and vomiting. The last four of these symptoms are more apt to be found in the vagotonic patient, who is said to be cold-blooded and reserved, and often to have a low blood pressure, contracted pupils, deep-set eyes, slow pulse and a sensitive oculocardiac reflex. He has a tendency to gastric hyperacidity, nausea and vomiting, and his cool, pale skin sweats easily. Respiratory arrhythmia, asthma, spastic constipation, high sugar tolerance and eosinophilia are said to be common among vagotonic patients.[35] The vagus may predominate in the profound degrees of alkalosis because of sympathetic depression.

The paresis of the posterior extremities observed by Frouin [5] in dogs suggests that the hypochloremia profoundly affected the spinal cord. The sympathetic centers in the intermedio-lateral columns may be affected by the same process. Several of my patients were given tincture of belladonna, but only in case 3 were there effects from atropine, as was indicated by a dry throat. I am sure that belladonna played little part in the production of the symptoms noted.

In acute hyperchloremia the tight feeling in the chest and the contraction of the throat may result from marked stimulation of the vagus, reminding one that the vagotonic patient is prone to have asthma. In chronic hyperchloremia, I do not believe that the vomiting, sinus bradycardia and lower blood pressure are due to vagus stimulation alone, although the vagotonic patient has a tendency to nausea and vomiting, slow pulse and low blood pressure. I do not know whether kidney dysfunction is primary or secondary, but surely it is aggravated and prolonged by the overload of chlorides.

In patients with definite hypochloremia (below 420), there were lassitude, restlessness, a dull feeling in the head, irritability, distaste for food, nausea and vomiting, dulness, weakness, "shaky sensations," and

34. Purves-Stewart: Diagnosis of Nervous Diseases, ed. 6, London, Edward Arnold and Company, 1924, p. 445.

35. Eppinger and Hess: A Clinical Study in Vegetative Neurology (Monograph on Vagotonia), New York, Nervous and Mental Disease Publishing Company.

in one case a craving for salt. The secretion of acid was diminished and the volume of secretion seemed to be lessened. In chronic alkalosis, there were weakness and cramps in the legs, diarrhea, dyspnea on exertion and other signs of weakness. Frouin,[5] experimentally, obtained lassitude, irritability, loss of appetite, dulness, muscular weakness, achlorhydria, trembling, paresis of the posterior extremities, convulsions with fits of anger and diminished volume of gastric secretion. What a close parallel to the symptoms found in clinical cases, even to the achlorhydria toward which case 3 was progressing rapidly when salt solution was given! If one allowed the hypochloremia to become profound enough or last long enough one might get paresis of the legs and tetany.[8] When p_H readings were taken, they ranged from about 7.52 to 7.64 (the upper limit of normal being 7.47 [15]), and thus were well below 7.8, the point at which tetany occurs.[19]

The question of the salts most useful in alkali treatment has been reviewed in this study. Potassium salts [36] may at once be dismissed because of their toxicity and high cost. Sodium salts have already proved their value, but in spite of the fact that soda gives more rapid relief, its action is not so prolonged, it seems to produce diarrhea in some cases and it is so readily absorbed that it appears to produce alkalosis more easily.[37] The importance of sodium chloride has already been discussed.

Calcium salts have proved their usefulness, but are not without fault. In spite of the fact that the carbonate is said not to be so readily absorbed,[37] it can produce alkalosis on doses little, if any, higher than those with the mixed powders of Sippy (neutralizing power of calcium carbonate two and a half times that of soda). I have no comparative studies to show the relative ease with which each salt might produce alkalosis in a given case. Several times at this hospital I have noted calcified concretions in the appendixes of patients who have taken calcium carbonate for gastro-intestinal conditions. Although most of the calcium is said to be excreted in the stools, some of Jordan's cases [7] showed distinct rises of blood calcium. Perhaps these are the persons in whom alkalosis from calcium carbonate is more prone to develop.

This salt is said to have a constipating action; however, this fact is denied by Loevenhart and Crandall.[38]

In spite of objections, I believe calcium carbonate is to be preferred. When I compare cases 3, 4 and 6 with cases 1, 2 and 5, I believe that alkalosis occurs less readily by the omission of soda. Surely, the hypo-

36. Sollman (footnote 28, page 787).

37. Loevenhart, A. S., and Crandall, L. A.: Calcium Carbonate in Treatment of Hyperacidity, J. A. M. A. **88**:1557 (May 14) 1927. Myers and Gatewood (footnote 17).

38. Loevenhart and Crandall (footnote 37, first reference).

chloremia seems to be less and the symptoms of alkalosis not as acute. Perhaps the chlorides were made more stable by the use of calcium carbonate alone. Perhaps calcium salts might help to prevent tetany,[8] for de Geus [39] did not obtain tetany with a blood calcium above 8 mg. per hundred cubic centimeters unless there was an excess of sodium. This means that if attempts are made to treat medically persons who have the milder degrees of pyloric obstruction, it is best to omit sodium bicarbonate, and that it would be justifiable to use small amounts of calcium chloride with the sodium chloride and dextrose in severe cases in which the patients are being prepared for operation.

Other arguments for the use of calcium carbonate are its greater and more prolonged neutralizing power. In spite of still greater neutralizing power and laxative properties, magnesium oxide should be condemned for use in the powders. With its use I have had irritable colon and chronic colitis develop in cases in which they did not exist before. Other means should be used to keep the bowels regular, such as mineral oil, stimulating enemas of cool water or oil retention enemas, suppositories, and, later in the treatment, additions to the diet.

With regard to the most desirable acid radical in the alkaline salts, the carbonates have been the most favored, as well they might be. They are less toxic and more effective than others which might be used. Phosphates have been used, but have given only fair results because of their extremely low neutralizing value and very slow action.[40] Citrates have been used in very small doses in the treatment for peptic ulcer.[41]

Both acid and basic chlorides are lost in aspirations and vomiting. Sodium chloride can therefore make up only part of the deficit, and thus accounts for the partial success in depletion (table 1). Youmans [42] and others have used ammonium chloride, theoretically the ideal salt, because the liver converts the ammonium ion into urea, leaving the chloride ion free to make up the disproportionate deficit of chloride. But this action of the liver protects the body against the toxic ammonium ion which makes patients with alkalosis feel worse. Given by mouth the general circulation is better protected, but the nauseating taste contraindicates its use by this route. The livers of patients with ulcers are frequently damaged and I believe it unwise to impose this extra burden. A patient with sprue (?) with alkalosis complained of severe contraction and burning of the throat, and said "everything turned

39. De Geus, J. G. F.: Tetany and Alkalosis, Nederl. maandschr. v. Geneesk. **13**:361, 1926; abstr., J. A. M. A. **86**:1955 (June 19) 1926.

40. Shattuck, H.F.; Rohdenburg, E. L., and Booher, E. E.: Antacids in Medical Management of Ulcer, J. A. M. A. **88**:200 (Jan. 19) 1924.

41. Vanderhoof, D.: Medical Cure of Duodenal Ulcer, J. A. M. A. **89**:344 (July 30) 1927.

42. Youmans, J. B., and Green, F. W.: Treatment of Gastric Tetany with Ammonium Chloride, J. A. M. A. **84**:808 (March 14) 1925.

black" when she was given ammonium chloride intravenously according to the method of Youmans. There may be a judicious balance between sodium and ammonium chlorides, permitting their use together with better results than either one singly.

Calcium chloride must be used judiciously—when used in the case just mentioned to stop tetany it produced burning of the hands, feet and rectum, a hot feeling all over, vomiting, grasping for breath, irregular pulse rate and for two days a lower range in temperature. On account of its disagreeable taste, I do not believe that calcium chloride should be given by mouth.

SUMMARY AND CONCLUSIONS

Much more work is needed to settle the questions raised by this study, but the following deductions are suggested by the observations thus far:

1. There must be a marked reduction of the chloride reserve in the body before gastric secretion is definitely affected, and then there is a drop in the free and the total acid without the reduction of the total chlorides, accompanied by the symptoms of alkalosis. The systemic action of the alkali used in the treatment for peptic ulcer apparently precipitates and aggravates this reaction. There is a vague suggestion of decreased volume of secretion. The acid secretion of patients with peptic ulcer cannot be controlled by restriction of the chloride intake.[43]

2. In cases of alkalosis without such profound depletion there is a suggestion of a similar phenomenon, particularly in the "fasting" contents.

3. A patient might remain on the Sippy milk diet indefinitely without chloride depletion, but in patients with nausea and vomiting, diarrhea or pyloric obstruction, one must take into account and make up the chloride deficit by giving sodium chloride if one expects the patient to continue to tolerate alkalis. Calcium and ammonium chlorides, if used at all, should be used sparingly and only after consideration of indications and contraindications in the individual case.

4. Alkali therapy might tend to decrease the free and the total acid secretion of the stomach while fasting, but longer periods of study are necessary to determine whether the gastric response to stimulation of food and alkali is definitely affected.

5. If it were possible to get samples of gastric contents free of mucus, saliva and duodenal regurgitation, one might get more definite relationships between total acid chlorides and total gastric chlorides, but present methods preclude this possibility.

6. A study of the relationship of the excretion of chloride to blood chlorides has not given a definite idea of the chloride reserve of the

43. Weitz, W., and Kissling, W.: Chlorides and Hyperacidity, München. med. Wchnschr. **72**:2177, 1925; abstr., J. A. M. A. **86**:455 (Feb. 6) 1926.

body, but the urine chlorides are markedly decreased when there is hypochloremia, which is an early sign of approaching alkalosis. Chloride excretion in the stools is negligible and does not suggest diminished absorption of chlorides from the use of calcium carbonate.

7. When the secretion of gastric acid is reduced in hypochloremia, the ratio of cell to plasma chlorides is reduced. A similar reduction of tissue cell to tissue fluid chloride, especially in sensitive nerve cells, may be the basis of the symptoms of alkalosis. I therefore, feel justified in ascribing symptoms to the effect of the hypochloremia which is a common accompaniment of uncompensated alkalosis—only one of my patients failed to have low blood chloride values, and here the picture was not clearcut on account of the symptoms of accompanying conditions.

8. In hypochloremia there may be a normal carbon dioxide capacity of the plasma with symptoms commonly ascribed to alkalosis. Therefore, the carbon dioxide capacity is not a reliable index of alkalosis. When determinations of the carbon dioxide capacity and content are taken simultaneously, the former is a little bit the higher. Both are elevated in profound or prolonged hypochloremia with a proportionately greater difference between the two. The p_H is increased.

9. The occasional patients reacting to alkali therapy with hypochloremia and normal carbon dioxide capacity commonly have functional gastro-intestinal disturbances and probably have unusually sensitive vegetative nervous systems.

10. In one of these cases, sodium chloride given intravenously promptly cleared up the symptoms of alkalosis. In patients with chloride depletion the results are not so clearcut, and in a patient with normal blood chlorides the results were disappointing.

11. Patients with hypochloremia with symptoms of alkalosis were noted by the neuropsychiatrist to be "sympathicotonic," or to have "probable dysfunction of the vegetative nervous system." Symptoms of hypochloremia and alkalosis may be explained on the basis of primary stimulation of the sympathetic nervous system followed by depression in the more toxic states.

12. Some symptoms, such as weakness and cramps in the legs, with the previously mentioned condition of the vegetative nervous system suggest toxic action on the lateral columns and funiculi of the spinal cord.

13. Even patients with partial pyloric obstruction respond very well to the Sippy alkali treatment. I believe his general plan of treatment to be without a peer, and consider calcium carbonate used alone the alkali of choice. From six to eight weeks of intensive therapy with gradual reduction of powders and return to normal diet in about a year seems to suffice if all foci of infection are cleared up.

CUTANEOUS AND VENOUS BLOOD SUGAR CURVES

II. IN BENIGN GLYCOSURIA AND IN DIABETES *

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As early as 1856, Chauveau [1] reported that there was more dextrose in arterial than in venous blood. Although his observations were known to Bang [2] and have been amply confirmed by subsequent investigators,[3] their implications have been almost entirely overlooked by most clinical observers, especially in this country.

It has been definitely established by Hagedorn,[4] Foster [5] and others that in the normal person in the postabsorptive state arterial (or cutaneous [6]) and venous blood differ little, if at all, in their sugar content. After a meal containing carbohydrate, however, the sugar curve of the arterial blood rises more than that of the venous blood. A definite positive arterial-venous difference is established. This difference is the most direct evidence that the tissues are actively removing dextrose from the blood and that this process of removal is rapid enough to be easily measurable.

In an earlier communication,[7] we described a procedure for the determination of alimentary cutaneous and venous blood sugar curves and its application to certain clinical and physiologic problems. Venous and cutaneous bloods, obtained as nearly simultaneously as possible,

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1. Chauveau: Compt. rend. Soc. de biol. **42**:1008, 1856.

2. Bang, Ivar: Der Blutsucker Wiesbaden, 1913.

3. Hagedorn, H. C.: Ugesk. f. Laeger **82**:796, 1920. Foster, G. L.: J. Biol. Chem. **55**:291 and 303, 1923. Holst, J. E.: Hospitalstid., Copenhagen, 1922, vol. 65, p. 577. Lawrence, R. D.: Brit. M. J. **1**:516, 1926. Rabinowitch, I. M.: Brit. J. Exper. Path. **8**:76, 1927. Friedenson, Myer; Rosenbaum, M. K.; Thalheimer, E. J., and Peters, J. P.: Cutaneous and Venous Blood Sugar Curves: I, J. Biol. Chem. **80**:269, 1928.

4. Hagedorn (footnote 3, first reference).

5. Foster (footnote three, second reference).

6. Both Hagedorn and Foster have shown that as far as sugar content is concerned arterial and cutaneous blood are practically identical.

7. Friedenson, Rosenbaum, Thalheimer and Peters (footnote 3, sixth reference).

were analyzed for dextrose by a micromodification of Benedict's [8] blood sugar method, reported in 1925, before, and at half hour intervals after, a meal consisting of either 50 Gm. of dextrose or mixed foods containing from 75 to 110 Gm. of carbohydrate. The effects of the two types of meals were not distinguishable.

It was found that the arterial-venous difference during fasting was usually negligible, but might be considerable. If a difference did occur it was usually positive (arterial > venous), although negative (venous > arterial) differences were occasionally observed. At either thirty or sixty minutes after the meal, or both, a positive difference, varying in magnitude from 6 to 50 mg. per hundred cubic centimeters, was always encountered, generally coinciding with the highest blood sugar determination. This difference was found even when hyperglycemia was minimal. After ninety minutes, when two thirds of the curves had returned within the normal fasting range, the arterial-venous difference had usually disappeared and occasionally had become negative.

It was found that insulin, given to a normal person during fasting, usually caused a demonstrable positive difference during the hypoglycemic state.

A group of patients with disease of the liver showed excessive or prolonged hyperglycemic reactions, but normal arterial-venous differences. This was interpreted as evidence of impairment of the ability of the liver to remove dextrose from the blood for storage as glycogen, without disturbance of the mechanism for the mobilization of dextrose into the muscles and other tissues.

Holst [9] and Lundsgaard and Holboll [10] claimed that the arterial-venous difference cannot be demonstrated in diabetic patients after meals, but is restored by the administration of insulin. Rabinowitch [11] showed that this is not an absolute distinguishing feature of diabetes. He found differences in certain mild cases of diabetes. These differences, however, were in general smaller than normal, and were often entirely lacking.

In the present paper are described the arterial (cutaneous) and venous blood sugar curves of diabetic persons, with and without insulin therapy, and of patients with glycosuria of doubtful nature.

Chart 1 shows sixteen experiments on fourteen patients with so-called benign glycosuria. One patient (case 12) has not returned for observation. The fact that he had hyperglycemia during fasting and excessive alimentary hyperglycemia suggest that he was diabetic in spite of the fact that the curve returned to a normal or relatively hypoglycemic level

8. Benedict, S. R.: J. Biol. Chem. **64**:207, 1925.
9. Holst (footnote 3, third reference).
10. Lundsgaard, C., and Holboll, S. A.: J. Biol. Chem. **65**:323, 1925.
11. Rabinowitch (footnote 3, fifth reference).

at the end of ninety minutes. EV (case 7) evidently developed an excessive prolonged hyperglycemia after the ingestion of food, and the glycosuria was not entirely unresponsive to dietary influences. Nevertheless, even in the postabsorptive state, when the blood sugar was within the normal fasting range, sugar was found in the urine. The

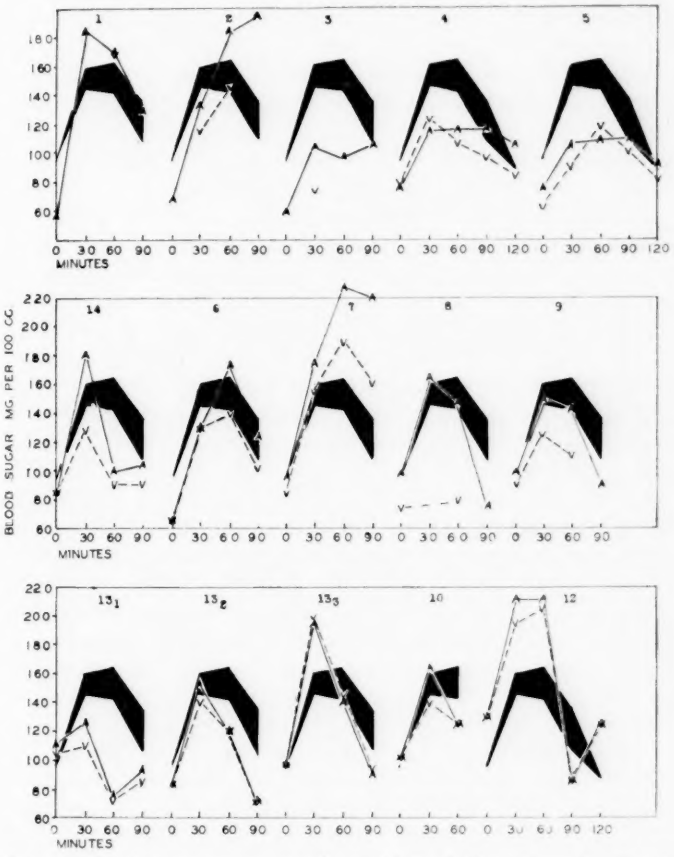

Chart 1.—Blood sugar curves of patients with borderline glycosuria. A—A and V—V represent cutaneous and venous blood sugar curves, respectively. The solid area shows the normal limits as determined in this laboratory (Benedict: J. Biol. Chem. **64**:207, 1925). The upper border of the area gives the highest observed cutaneous values; the lower border, the highest observed venous values. The case numbers are given above the curves.

long duration of the glycosuria without the appearance of diabetic symptoms and its relative failure to respond to dietary measures are evidence that it is nondiabetic and belongs to the class of "cyclic renal

glycosurias" described by Hatlehöl.[12] All these patients, whether diabetic or not, developed distinct arterial-venous differences.

Only one case of the group (RW, case 5), seems rightfully to belong in the class of renal glycosurias. Although this patient's curve is somewhat prolonged, it never rises above the range of normal alimentary hyperglycemia. Nevertheless, he showed glycosuria both before and after the meal. He developed a small, but distinct, arterial-venous difference at the end of thirty minutes. If only the venous curves of cases 14 and 6 were taken into consideration, it would be easy to conclude that the hyperglycemic reactions were normal. If glycosuria had occurred, it would have been as easy to conclude that it was of renal origin. However, the arterial curves in both cases rose distinctly higher than those of the normal persons in whom investigations were conducted by the same method.

It must be obvious that, if an arterial-venous difference is characteristic of the alimentary hyperglycemic reaction, a diagnosis of "renal glycosuria" cannot be made from studies of venous blood sugar alone, as has been the custom in this country. This is especially true if the glycosuria is of the cyclic type, i.e., if it occurs only after the ingestion of carbohydrate. It is presumably the concentration of dextrose in the blood that goes to the kidneys and not that which comes from the tissues that determines the excretion of sugar in the urine. Hatlehöl[12] also called attention to the fact that the peak of alimentary hyperglycemia may be extremely evanescent. It is, therefore, necessary not only to examine cutaneous blood, but to examine it at short intervals (every two to ten minutes) to establish a diagnosis of cyclic renal glycosuria in a person who does not show glycosuria in the postabsorptive state.

It is also evident that certain subjects may, without the appearance of glycosuria, develop excessive or prolonged alimentary hyperglycemic reactions that manifest themselves only in the cutaneous blood sugar curves.

According to all the usual criteria, the patient in case 13 had benign glycosuria. Over a period of more than three years, sugar was found in the urine at intervals after meals; however, he never had symptoms of diabetes. The blood sugar during fasting was repeatedly determined and almost invariably fell within the normal range, although his diet was never restricted. In the three studies made on this subject, the alimentary hyperglycemic reaction was completed within ninety minutes, and in only one did the blood sugar reach an excessively high level. In spite of all these indications that the glycosuria was benign and not of the diabetic type, he developed little arterial-venous difference. In fact,

12. Hatlehöl, R.: Acta med. Scandinav., 1924, supplement 7.

at the time he had the excessive hyperglycemia, he presented a persistent negative difference. Current theories, which hold that insulin affects especially the mobilization of sugar into and its utilization by the tissues, would lead one to conclude that these phenomena were evidences of a true diabetic state or lack of insulin. In the postabsorptive state, when the subject was given 10 units of insulin a striking degree of hypoglycemia and distinct symptoms of insulin shock develop, manifestations of an unusual susceptibility to the pancreatic hormone. Two hours after the dose of insulin and after he had taken considerable carbohydrate to overcome its effect, he showed moderate hyperglycemia and a positive arterial-venous difference of 25 mg.

The simultaneous studies of cutaneous and venous blood sugar curves have not, therefore, proved of great assistance in differentiating benign from diabetic glycosuria. They have demonstrated that determinations of the cutaneous blood sugar are of more value than those of the venous blood sugar in such differentiation. In fact, it is doubtful whether much significance can be attached to venous curves unless they show definite hyperglycemia. Certainly, determinations of the cutaneous blood sugar are far more reliable diagnostic measures.

Chart 2 presents the results of fifteen studies of ten patients with diabetes. Cutaneous and venous curves were obtained usually after the ordinary mixed breakfast of the diabetic diet. In two mild cases, 50 Gm. of dextrose was given instead. In only two instances did the patients exhibit a significant degree of glycosuria, although none received insulin during the test. All the subjects had definite hyperglycemia during fasting, in spite of the fact that they had been on limited diets before the experiments.

All but two of the subjects showed large arterial-venous differences after meals. The two who failed to show such differences were, oddly enough, those with the smallest hyperglycemic reactions and with decreased blood sugar during fasting (cases 17 and 18). The magnitude of the arterial-venous difference cannot be used, therefore, as a criterion of the severity of a diabetic condition, nor is the failure to show such a difference characteristic of diabetes.

It is interesting to note that in the two mild cases of diabetes mentioned, cases 17 and 18, improvement of the diabetic condition was marked by an increase in the arterial-venous difference rather than by any change in the degree or duration of the arterial hyperglycemic reaction. In case 19, with improvement the difference increased, and the hyperglycemia diminished.

Although large arterial-venous differences occurred in the most extreme hyperglycemic reactions, they presented certain peculiar characteristics not observed in normal persons, borderline cases or extremely mild cases of diabetes. In cases 23 and 24 the curves showed

differences of considerable magnitude at the end of thirty minutes. At the end of sixty and of ninety minutes, these differences had been almost entirely abolished, although the arterial hyperglycemia had not diminished or had even increased. The ability of the tissues to remove sugar from the blood in these patients, although not entirely lost, appeared to be limited in extent and was rapidly exhausted.

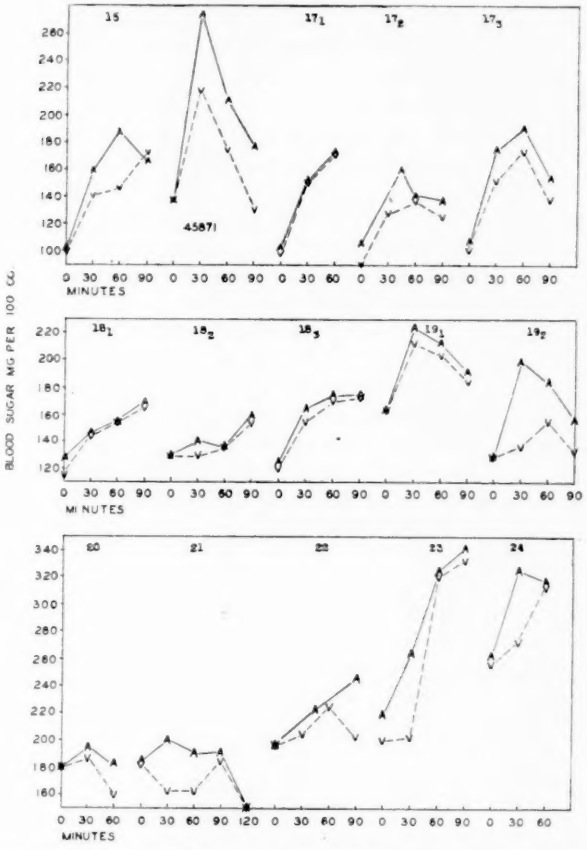

Chart 2.—Blood sugar curves of diabetic patients. A—A and V—V represent cutaneous and venous blood sugar curves, respectively. The case numbers are given above the curves.

In mild diabetes, then, the ability of the tissues to remove sugar from the blood, as evidenced by the development of an arterial-venous difference after meals, is seldom abolished. It is usually apparent only at a higher blood sugar level than that required to produce it in the normal

person. If this were not the case, arterial-venous differences during fasting would be observed more often. In some instances, it seems to be more rapidly exhausted than normally. Even in the diabetic patient, it is impossible to determine renal thresholds or the degree or extent of hyperglycemic reactions from studies of the venous blood alone.

Table 1 illustrates the effects of insulin followed by a meal on the cutaneous and venous blood sugar of patients with diabetes of variable severity, but sufficiently grave to require treatment with insulin. The blood sugar measurements were taken at different intervals after doses of insulin and after breakfast. Both the insulin dosage and the meals were those which the patients were regularly receiving at the time of the observations on the blood sugar. In only one instance, case 27, did appreciable glycosuria result, and in no case did the blood sugar fall to hypoglycemic levels during the period of observation.

With the exception of case 28, the diets varied but little: carbohydrate from 33 to 51, protein from 19 to 23 and fat from 41 to 65 Gm. The insulin dosage, however, varied from 5 to 45 units. Although the doses, judged by their effects on glycosuria and glycemia, seemed to be well adjusted to the needs of the patients,[13] they bore no relation to the blood sugar level during fasting. This is only one illustration of the now well recognized fact that insulin dosage cannot be calculated in advance from either the blood sugar level or the diet, or both, but must depend on the nature of the disease in the given person.

Positive arterial-venous differences during fasting were encountered with far greater frequency in this group of patients than in normal persons, patients with borderline glycosurias or even mild cases of diabetes. Lawrence[14] reported similar results. This is strangely at variance with the generally accepted view that the most characteristic functional disturbance in diabetes is an impairment of the ability of the tissues to remove dextrose from the blood and utilize it. Such large arterial venous differences can mean only that the tissues are actively absorbing sugar. If the figures are carefully analyzed, there seems to be a tendency for large differences to occur more frequently in patients with high blood sugar levels during fasting. This is clearly brought out by the figures compiled in table 2 from the studies of all the patients with diabetes.

From the data in table 2, one might infer that the diabetic patient has not lost the power of mobilizing dextrose into the tissues, but requires a higher concentration of sugar in the blood to activate the mechanism for the removal of dextrose. When the blood sugar rises

13. Case 27 is an exception. On the day of the test, a rapidly spreading cellulitis developed in a gangrenous foot, necessitating a rapid increase of the insulin dosage.

14. Lawrence (footnote 3, fourth reference).

TABLE 1.—*Effects of the Administration of Insulin Followed by a Meal in Patients with Diabetes* *

Time, Minutes	Case 19 Arterial	Case 19 Venous	Case 19 Difference	Case 22 Arterial	Case 22 Venous	Case 22 Difference	Case 22 Arterial	Case 22 Venous	Case 22 Difference
0	151	138	13	160	160	0	187	187	0
	Insulin, 10 units			Insulin, 20 units			Insulin, 20 units		
30	141	138	33	110	97	13	129	129	0
	Protein..... 23			Protein..... 20			Protein..... 19		
	Fat..... 52			Fat..... 53			Fat..... 62		
	Carbohydrate.. 33			Carbohydrate.. 41			Carbohydrate.. 51		
60	148	142	6	82	72	10	135	128	7
90	133	128	5	74	...	..	120†	124	..
120	144	131	13	...	...	..	106	91	15
Urine sugar	.....			Overnight.....		0	Overnight.....		0
	.....			7-11 a.m.....		0	7-11 a.m.....		0
	Case 25			Case 26			Case 27		
0	161	119	42	195	195	0	177	174	3
	Insulin, 45 units			Insulin, 10 units			Insulin, 5 units		
30	131	126	5	169	169	0	177	184	—7
	Protein..... 22			Protein..... 20			Protein..... 22		
	Fat..... 65			Fat..... 42			Fat..... 41		
	Carbohydrate.. 41			Carbohydrate.. 33			Carbohydrate.. 34		
60	...	...	..	217	186	31	...	...	..
90	149	123	26	...	...	..	234	230	4
120	74	89	—15	205	180	25	...	...	..
150	...	...	..	...	...	..	237	237	0
180	103	95	8	...	...	..	159	152	6
Urine sugar	Overnight.....		±	Overnight.....		0	.....		
	7-11 a.m.....		0	7-11 a.m.....		0	.....		
	Case 28			Case 29			Case 27		
0	195	190	5	209	183	26	227	211	16
	Insulin, 50 units			Insulin, 30 units			Insulin, 45 units		
30	...	...	..	200	185	15	216	229	—13
				Protein..... 23			Protein..... 21		
				Fat..... 42			Fat..... 51		
				Carbohydrate.. 33			Carbohydrate.. 33		
60	151	134	17	211	150	61	...	...	..
	Protein..... 23								
	Fat.....100								
	Carbohydrate..100								
90	...	...	..	...	...	..	261	266	— 5
120	125	121	4	147	111	36	...	...	..
150	...	...	..	...	...	..	281	292	—11
180	103	95	8	...	...	..	...	...	..
Urine sugar	Overnight.....		+	Overnight.....		0	Overnight, complete reduction		
	7-11 a.m.....		0	7-11 a.m.....		0	7-11 a.m., complete reduction		
	Case 30			Case 31					
0	237	227	10	263	273	—10			
	Insulin, 20 units			Insulin, 15 units					
30	206	199	7	234	250	—16			
				Protein..... 20					
				Fat..... 42					
				Carbohydrate.. 33					
60	225	172	54						
	Protein..... 20								
	Fat..... 49								
	Carbohydrate.. 33								
90	...	...	..	283	238	45			
120	167	160	7	...	...	..			
150	...	...	..	220	214	6			
180	159	152	6	..	...	..			
Urine sugar	Overnight.....		0	Overnight.....		0			
	7-11 a.m.....		±	7-11 a.m.....		0			

* Insulin was given immediately after the first estimation of blood sugar was taken (calculated in mg. per hundred cubic centimeters); breakfast was given immediately after the thirty or sixty minute estimates of blood sugar, as indicated.

† One hundred and five minutes.

above this concentration, a positive arterial-venous difference appears whether the hyperglycemia follows the ingestion of food or develops during the fasting state. There are, of course, exceptions to the rule; for example, the patient in case 32, who had the highest observed hyperglycemia during fasting, exhibited a negative difference. One would expect such variability. In this case, the threshold for the activation of the mechanism for the removal of sugar may have been still higher.

A definite positive difference was established after doses of insulin and a meal in nine of eleven instances. In one no difference was observed and in another negative differences only. In only five experiments was a significant difference found after the administration of insulin alone. It cannot be inferred from this, however, that insulin failed to produce such a difference. In all but two experiments, breakfast was given thirty minutes after doses of insulin; in these two it

TABLE 2.—*Study of Patients with Diabetes*

Number of Observations	Fasting Cutaneous Blood Sugar	Arterial-Venous Difference		
		Maximum	Minimum	Average
16	> 181	15	— 1	4
9	< 180	42	—10	10
11	> 181	> 5		
5	> 181	< 4		
3	< 180	> 5		
6	< 180	< 4		

was withheld for an hour. In both the latter, cases 28 and 30, a large difference was produced at the sixty minute period. It seems not improbable that an interval of more than thirty minutes is required before the action of insulin becomes evident in the arterial-venous difference.

In spite of the fact that an arterial-venous difference became evident usually only after more than thirty minutes had elapsed, a distinct decrease in blood sugar was demonstrable almost invariably at the thirty minute point. This might be interpreted as an indication that the initial action of insulin is exerted on the liver and not on the tissues. Such a conclusion, however, must be accepted with caution. Undoubtedly, all the reactions involved in the disposal of carbohydrate are in mutual chemical and physiologic equilibrium. Changes in the system are only relative and not absolute. Diminution of the destruction of hepatic glycogen will have the same apparent effect, for example, as the increased formation of hepatic glycogen. It may be that insulin, by rendering carbohydrate available to the tissues, removes the stimulus which has in the diabetic patient led to hepatic glycogenolysis and the consequent production of hyperglycemia. It also accelerates the combustion

and storage of carbohydrate in the tissues. There may be, however, such a large excess of sugar available in these tissues that, for a time, it is unnecessary to draw on the store of blood sugar sufficiently to produce a perceptible arterial-venous difference.

Such an explanation would suffice for most of the experiments. At first sight it is hardly satisfactory in the instance of case 27, in which there was a continuously negative difference. On the day of the experiment, in this case, rapidly spreading cellulitis developed, attended by a sudden reduction of carbohydrate tolerance. Forty-five units of insulin, which had proved an adequate dose previously, was totally ineffectual in checking glycosuria on this day. The negative difference, then, is an expression of the absence of the effect of insulin. Under these circumstances, apparently, the tissues lose sugar to the blood, a phenomenon which, although contrary to physiologic conceptions of carbohydrate metabolism, has been noted in other connection in these studies.[8]

SUMMARY AND CONCLUSIONS

Arterial (cutaneous) and venous blood sugar curves have been studied after the administration of dextrose or mixed meals in patients with nondiabetic glycosuria and with diabetes, with and without insulin therapy.

The presence or absence of a positive arterial-venous blood sugar difference after meals cannot be used to distinguish benign glycosuria from diabetes.

In patients with benign glycosuria, the arterial-venous difference may be so great that the venous blood sugar, determined at thirty minute intervals, may never show hyperglycemia that is strikingly evident in the venous sugar curve. For the differentiation of types of benign glycosuria, venous sugar curves are of little value.

In mild diabetes, arterial-venous differences can usually be demonstrated at an abnormally high level.

After the administration of insulin, such differences develop at lower levels. Insulin, however, may lower the blood sugar level without causing an appreciable difference.

REPORT OF CASES

CASE 1.—A girl, aged 4, was admitted to the hospital on Aug. 1, 1927; in June, 1927, her mother had noted slight polydipsia, and frequency of urination and glycosuria were discovered. One maternal aunt was known to have diabetes.

Physical examination revealed nothing of significance except adhesions of the labia minora and slight vaginal discharge, in which no gram-negative diplococci were found.

On diets containing 35 Gm. of protein, from 85 to 115 Gm. of fat and from 70 to 75 Gm. of carbohydrate, all samples of urine gave from ± to 2 + reactions with Benedict's test and from ± to + nitroprusside tests for acetone. Increasing

the diet to 250 Gm. of carbohydrate had no apparent effect on the glycosuria. When from 5 to 10 units of insulin were given before breakfast, early morning samples continued to be from ± to 2+, but the patient remained free from glycosuria throughout the day.

The blood sugar levels during fasting were: August 3, 70 mg. per hundred cubic centimeters; August 11, 97 mg.; August 31, 65 mg.

After being discharged from the hospital on September 1, the patient continued to show from ± to + reactions with Benedict's test on a diet in which the carbohydrate was allowed to increase to 200 Gm. or more. The glycosuria did not become greater, nor had diabetic symptoms appeared on this regimen by June, 1928. The dextrose tolerance test was made on Aug. 16, 1927, but was not complete because difficulty was experienced in obtaining samples of venous blood.

The diagnosis was "borderline" glycosuria (diabetes?).

CASE 2.—H. R., a boy, aged 12, first seen in the clinic on July 12, 1927, had been troubled for many years with attacks of hay-fever, during some of which a slight degree of glycosuria was noted. Diabetic symptoms never developed, but his mother restricted the carbohydrate of his diet, believing that this relieved the hay-fever. His father was mildly diabetic, and a maternal uncle, who proved to have hemochromatosis, had died in diabetic coma during an attack of lobar pneumonia.

TABLE 3.—*Results of Benedict's Test*

	7-11 a.m.	11-4 p.m.	4-9 p.m.	9-7 a.m.
Feb. 5 on an unlimited diet	..	4+	Complete reduction	4+
Feb. 6, protein, 90 Gm.; fat, 200 Gm.; carbohydrate, 200 Gm.	±	Complete reduction	4+	2+
Feb. 7, protein, 90 Gm.; fat, 200 Gm.; carbohydrate, 200 Gm.	Complete reduction	Complete reduction		

A dextrose tolerance test was made on February 7.

Physical examination gave essentially negative results.

On July 18, the blood sugar during fasting was 82 mg. per hundred cubic centimeters. While on a diet estimated to contain 80 Gm. of protein, 125 Gm. of fat and 165 Gm. of carbohydrate, urinalyses showed: on July 17, at noon, Benedict's reaction, 0; 6 p. m., +; 10 p. m., ±; July 18, 8 a. m., 0.

A test for sugar tolerance was made on July 22. After this, the patient became and remained continuously aglycosuric on a diet containing 75 Gm. of protein, 125 Gm. of fat and 175 Gm. of carbohydrate. In October, 1927, he was still aglycosuric, although he frequently overstepped his diet.

The impression was that the condition was benign glycosuria.

CASE 3.—A youth, aged 19, a college student, in whom glycosuria had been discovered in September, 1926, on routine examination of the urine by the university health department, was admitted to the hospital on Feb. 5, 1927. Weekly examinations showed that the glycosuria was persistent. It was not eliminated in a week, with the patient on a diet containing no obvious sweets nor starchy foods. The patient never had diabetic symptoms. One brother was under treatment for glycosuria.

Physical examination revealed no abnormalities.

The diagnosis was: benign glycosuria (renal ?).

CASE 4.—A man, aged 37, a Jew, married, was admitted to the hospital on May 2, 1927, complaining of symptoms suggesting intermittent claudication except

that weakness was more evident than pain. No objective manifestations of neurologic or vascular disturbances were discovered.

When the patient was on a regular diet, glycosuria did not appear. A dextrose tolerance test was made on May 7 to determine whether the patient had the reduced carbohydrate tolerance usually found in thrombo-angiitis obliterans.

The diagnosis was: no disturbance of carbohydrate metabolism.

CASE 5.—R. W., a man, aged 36, first seen in the clinic in May, 1926, reported that nine years earlier, when he applied for insurance, examination disclosed a trace of sugar in the urine. This condition continued in spite of a moderate restriction of the diet.

A dextrose tolerance test was made on May 3, 1926.

On March 3, 1927, he returned to the clinic with glycosuria, but without diabetic symptoms, on an unrestricted diet.

After the ingestion of 100 Gm. of dextrose, a dextrose tolerance test made by an insurance company on Jan. 24, 1927, showed the results given in table 4.

The impression was that the condition was benign glycosuria (renal?).

CASE 6.—A woman, aged 25, was admitted to the hospital for twenty-four hours on Sept. 8, 1926, shortly after she had reported to the dispensary complaining of excessive menstrual pain. Glycosuria was discovered. She entered the hospital on Sept. 8, 1926, for a dextrose tolerance test. After this time, she remained

TABLE 4.—*Results of Folin-Wu Test*

Time	Venous Blood Sugar	Urine Sugar, per Cent
1:45 p.m. (fasting)	102	0.00
3:10 p.m.	130	0.75
3:45 p.m.	130	0.55

aglycosuric on a diet containing 70 Gm. of protein, 175 Gm. of fat and 150 Gm. of carbohydrate. On Oct. 29, 1927, an exploratory operation revealed that the left kidney was ectopic and lying in the pelvis. Appendectomy and hysteropexy were performed. While the patient was in the hospital on a regular diet, glycosuria did not appear. The blood sugar during fasting on admission was 87 mg. per hundred centimeters.

The patient was not seen after being discharged from the hospital.

CASE 7.—E. V., a man, aged 42, was first seen in the clinic on May 18, 1928. Glycosuria had first been discovered in 1908, when the patient was operated on for hernia, and had been found at intervals ever since. He had been accepted, however, for service in the army in the Great War, at which time the urine was reported as normal. On two occasions, moderate dietetic restriction had affected the glycosuria but little. At no time had diabetic symptoms appeared.

During the winter of 1927 to 1928, he had been troubled with nervousness and exhaustion, especially marked before meals and relieved after the ingestion of food.

Physical examination gave essentially negative results. Urine passed in the clinic gave a 4+ Benedict reaction. A dextrose tolerance test was made on May 22.

Urinalyses showed: May 23, before lunch, Benedict's, ±; 4 p. m., +; 7 p. m., 3 +; 10 p. m., +; May 24, 7 a. m., +; 10 a. m., 4 +.

With a restriction of the diet to 90 Gm. of protein, 200 Gm. of fat and 150 Gm. of carbohydrate, variable, often considerable, amounts of sugar appeared in all samples.

The impression was that the condition was benign glycosuria (?).

CASE 8.—A man, aged 54, was admitted to the hospital on March, 12, 1928. Glycosuria had been discovered in 1918, when he was suffering from a carbuncle on the nose. In the intervening ten years, no diabetic symptoms had appeared, although he had dieted only at intervals and had then omitted only obvious sweets and starches. In the six months before admission, on such a regimen, he had lost 9 pounds (4.1 Kg.).

Physical examination gave essentially negative results.

While he was in the hospital, from March 12 to 19, the urine never gave more than a ± reaction with Benedict's solution. The diet, meanwhile, had been gradually increased from 60 Gm. of protein, 150 Gm. of fat and 125 Gm. of carbohydrate, to 80 of protein, 175 of fat and 175 of carbohydrate, equally distributed in the three meals. On March 18, 25 Gm. of dextrose was added to his breakfast without producing glycosuria.

A dextrose tolerance test was made on March 17.

The impression was that the condition was benign glycosuria.

CASE 9.—F. B., a man, aged 24, a medical student, was first seen in the clinic on Feb. 14, 1927. In 1917, he was found to have glycosuria, which cleared up after one week of moderate restriction of the diet. Shortly after this, a dextrose tolerance test was done, on the basis of which he was told that he did not have diabetes. No further urinalyses were made until 1927, when repeated tests again revealed a slight degree of glycosuria. At no time did he have diabetic symptoms. His past history was unimportant. His father was said to have "benign glycosuria," and at one time one brother had been temporarily refused life insurance because of glycosuria.

With the patient on a full diet, examinations of the urine showed: February 17, before lunch, Benedict's test, +; before supper, 2+; before bed, 2+; on February 18, before breakfast, 2+. No acetone was found in any of the samples.

On February 17, the blood sugar during fasting was 83 mg. per hundred cubic centimeters.

A dextrose tolerance test was made on February 20. No subsequent examinations have been made.

The diagnosis was benign glycosuria.

CASE 10.—A boy, aged 14, admitted to the hospital on Feb. 23, 1926, had fallen while skating on January 13. The fall dazed him, although he did not become unconscious. No fractures or lacerations were produced. On January 13, 14, 15 and 16, a slight degree of glycosuria was observed. Examination on January 19 and on February 1, however, revealed no sugar. On February 16, three hours after an ordinary breakfast, the blood sugar was 114 mg. per hundred cubic centimeters by the Folin-Wu technic. He had no diabetic symptoms at any time and no other symptoms after the first twenty-four hours.

Physical examination gave entirely negative results.

A dextrose tolerance test was made on February 25.

The impression was that the condition was symptomatic glycosuria, associated with concussion of the brain.

CASE 11.—A woman, aged 60, admitted to the hospital on Feb. 2, 1927, had been troubled with dizziness on exertion and polydipsia for one year. At the onset, she had transient glycosuria. One month before admission, polydipsia and polyuria had recurred, and sugar was again found in the urine. This condition again disappeared rapidly without treatment.

Physical examination revealed nothing of importance. For the first two days in the hospital, she had a slight febrile reaction. On February 3, the blood sugar

during fasting was 109 mg. per hundred cubic centimeters. On a diet of 60 Gm. of protein, 150 Gm. of fat and 100 Gm. of carbohydrate, the urine remained sugar-free continuously.

A sugar tolerance test was made on February 5; venous blood could not be obtained.

The impression was that the condition was early diabetes (?).

CASE 12.—J. H., a man, aged 38, was first seen in the clinic on Oct. 1, 1926, six months after he had been found to have glycosuria in the course of an examination made when he applied for insurance. During this time it had been found at intervals. On April 25, 1926, the blood sugar during fasting was 115 mg. per hundred cubic centimeters by the Folin-Wu method. From July 1 to October 1, he lived on a diet without sweets, potatoes and white bread. At no time had he developed diabetic symptoms. When dieting, but not before, he lost 8 pounds (3.6 Kg.). One brother was known to have had transient glycosuria.

The physical examination gave essentially negative results.

On October 1, after a period of dieting, the urine was sugar-free. He then resumed a normal diet. A dextrose tolerance test was made on October 10. After this time, on a diet containing 65 Gm. of protein, 150 Gm. of fat and 200 Gm. of carbohydrate, he remained aglycosuric even when he became careless and added

TABLE 5.—*The Results After Fasting and the Ingestion of Insulin*

	Arterial	Venous	Difference
Fasting	89	93	—4
30 minutes after insulin	68	74	—6
60 minutes after insulin	54	50	4

small extra portions of bread and fruit. The patient has not returned since the fall of 1926.

The impression was that the condition was mild diabetes.

CASE 13.—R. N., a physician, aged 25, was apparently in excellent health. On several occasions, dextrose was discovered in the urine. He had never had diabetic symptoms. Physical examination revealed no abnormalities other than a general tendency to vasomotor instability.

The first two tolerance tests were made in the fall of 1925. The third test was made on May 8, 1927.

The effect of 10 units of insulin on the same subject was studied a few days later and was reported in a previous article.[7]

At this point, he developed symptoms of insulin shock and in the course of the next forty-five minutes was given 100 cc. of orange juice, some dextrose and his regular breakfast. One hundred and twenty minutes after the ingestion of insulin, the arterial blood was 149 and the venous, 124, with a difference of 25.

CASE 14.—G. P., a woman, aged 65, with no symptoms of diabetes, had shown slight glycosuria at intervals for three months.

Physical examination revealed nothing important.

A carbohydrate tolerance test was made in April, 1926. During the succeeding two years, the patient lived on a normal diet without developing further glycosuria or any diabetic symptoms.

CASE 15.—A man, aged 57, was admitted to the hospital on Oct. 12, 1926, following a year of sleeplessness, blurring of vision and steady loss of weight. At the onset, he had slight polyuria and polydipsia. Repeated examinations of the urine had shown glycosuria on several occasions.

On September 14 and 21, when he was seen in the clinic, no sugar was found in the urine, and the physical examination was negative except for tachycardia, nervousness and evidence of loss of weight. On September 21, the blood sugar during fasting was 103 mg. per hundred cubic centimeters.

On September 23, he was suddenly seized with an attack of vomiting and diarrhea, and his temperature rose to 102 F. The temperature subsided rapidly, but the diarrhea persisted.

At the time of admission, he appeared emaciated and chronically ill. Blood culture was sterile. From the stools, dysentery bacilli of the Hiss and Strong group were isolated. At first, he had leukopenia with low grade fever, which condition gradually cleared up. No sugar was found in the urine, although the diet was gradually increased to: protein, 90 Gm.; fat, 200 Gm.; carbohydrate, 300 Gm., without insulin.

A tolerance test was made on October 31.

He was discharged on November 8.

CASE 16.—A woman, aged 22, was admitted to the hospital on Sept. 29, 1925, because of vomiting, apparently of psychoneurotic origin. On Nov. 27, 1926, she was again admitted because of an incomplete abortion. The same cause brought her to the hospital on Nov. 12, 1927. On the first two occasions, the urine, on several examinations, was free from sugar. At the time of the third admission, she had a moderate degree of glycosuria, polyuria and polydipsia. These conditions cleared up rapidly under dietetic treatment, and she was discharged on Dec. 21, 1927, aglycosuric on a diet of: protein, 60 Gm.; fat, 125 Gm., and carbohydrate, 175 Gm., without insulin.

Blood sugar during fasting was: November 17, 127 mg.; November 19, 75 mg. per hundred cubic centimeters.

A dextrose tolerance test was made on November 29.

CASE 17.—A man, aged 45, admitted to the hospital on Sept. 4, 1925, had been struck by an automobile, and sustained fractures of the tibia, fibula and radius. On admission, he appeared much shaken and somewhat shocked and had transient auricular fibrillation. Marked glycosuria was discovered which, at first, could be controlled only with 30 or 40 units of insulin on a diet of 80 Gm. of protein, 150 Gm. of fat and 125 Gm. of carbohydrate. His tolerance rapidly increased so that he was finally kept aglycosuric without insulin on a diet of: protein, 80 Gm.; fat, 150 Gm., and carbohydrate, 300 Gm. Tolerance tests with the patient on this diet were made on October 10 and 13 and November 6.

He was discharged from the hospital on November 7.

CASE 18.—A woman, aged 70, admitted to the hospital on Nov. 27, 1925, gave a history of polydipsia, polyuria and occasional incontinence of urine of from six to ten years' duration, increasing in severity. In 1920, she broke the left hip, and since then had been able to walk only with the aid of crutches. At this time, glycosuria was discovered. On Nov. 20, 1925, she slipped and fell; after this, frequency, incontinence and glycosuria grew worse and she became unable to walk.

On admission, she appeared emaciated and poorly cared for, presenting a crusted, desquamated, macerated area over the lower part of the back, and over the buttocks and the left thigh. She proved to have an ununited fracture of the neck of the left femur, slight cardiac decompensation and chronic cystitis, besides diabetes of moderate severity.

With nursing care, a restricted diet and administration of insulin, she improved rapidly. At first, 50 units of insulin was required to keep the urine sugar-free when she was on a diet of 60 Gm. of protein, 150 Gm. of fat and 100 Gm. of carbo-

hydrate. When she was discharged from the hospital on December 30, 30 units of insulin given daily before breakfast was sufficient with the same diet.

Tolerance tests were made on December 3, 8 and 15. On these days, insulin was omitted before breakfast and given before lunch instead. The diet, results of urinalyses and insulin dosage on these days are given in table 6.

Case 19.—A man, aged 38, was first admitted to the hospital on April 20, 1922. In 1920, blurring of vision, polyuria and polydipsia developed suddenly, and he lost 85 pounds (38.6 Kg.) in two months. Glycosuria was discovered and a diet prescribed to which the patient did not adhere.

In the hospital, his diet was gradually increased to protein, 60 Gm.; fat, 150 Gm., and carbohydrate, 300 Gm., without the appearance of glycosuria. After the ingestion of 75 Gm. of dextrose on May 3, the venous blood sugar, tested by Benedict and Lewis' trinitrophenol method, rose to 262 mg. per hundred cubic centimeters after two hours, and was still 136 mg. at the end of three hours. After two hours, the urine contained 2 per cent of sugar. On April 21, the blood sugar during fasting was only 158 mg.

On a diet of 100 Gm. of protein, 200 Gm. of fat and 200 Gm. of carbohydrate, to which he did not adhere continuously, he remained aglycosuric until Nov. 1, 1922, at which time he contracted a severe cold. On November 22, he entered the

Table 6.—*Diet, Urinalyses and Insulin Dosage*

Date	Diet			Urine, Benedict's Reaction				Insulin	
	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	A.M. 7–11	P.M. 11–4	P.M. 4–9	A.M. 9–7	Noon	P.M.
December 3	60	150	100	±	2+	0	0	30	10
December 8	60	150	100	0	2+	±	0	30	10
December 15	60	150	100	0	+	±	0	20	0

hospital where the urine became sugar-free only when the diet was reduced to 75 Gm. of protein, 150 Gm. of fat and 100 Gm. of carbohydrate. On November 23, the blood sugar during fasting was 231 mg. After being discharged from the hospital, he was able to increase his diet gradually to its original value, where it was maintained (with the exception of a short period in January, 1923, when he had furunculosis) until November, 1925, when he was admitted to the hospital on account of an infected foot and a cold. At this time, 10 units of insulin was required to keep the urine free from sugar on a diet of 75 Gm. of protein, 200 Gm. of fat and 125 Gm. of carbohydrate. On November 12, the blood sugar during fasting was 219 mg.

Tolerance tests were made on November 13, 19 and 24; their results are shown in table 1. The diets and results of urinalysis on these dates are shown in table 7.

After the patient was discharged from the hospital, the infection of the foot became worse and drainage was necessary. For a time, the dosage of insulin had to be increased; however, as the condition of the foot cleared up, he was able to reduce the dosage to 5 units daily and, in December, 1927, to omit insulin entirely for a while, with a diet of: protein, 75 Gm.; fat, 200 Gm., and carbohydrate, 125 Gm.

Case 20.—A woman, aged 74, admitted to the hospital on Oct. 1, 1925, had been troubled for two months before with polyuria, polydipsia and some dysuria, which conditions improved with dietetic regulation. In the last week of September, the left leg and foot became swollen.

On admission, she had moderate edema of the left leg and foot and evidences of subacromial bursitis on the right side. The blood sugar during fasting was 212 mg. per hundred cubic centimeters.

The diabetes was easily controlled without insulin, but with a diet of 60 Gm. of protein, 100 Gm. of fat and 125 Gm. of carbohydrate. The condition of the shoulder improved rapidly, and the edema, which was apparently due to thrombosis of varicose veins, subsided.

A tolerance test was made on October 8.

She was discharged from the hospital on October 15.

CASE 21.—A man, aged 42, was admitted to the hospital on April 15, 1927, six weeks after he noted general malaise, polyuria and polydipsia, with loss of weight. Ten days later he had vomited several times and, after that, rapidly lapsed into a semistuporous condition. Glycosuria had been discovered, and he had improved rapidly with insulin and dietary therapy. At first, 70 units of insulin was required daily; however, this dosage was rapidly reduced to 40 units. In the days preceding admission to the hospital, frequent insulin shocks had occurred.

Physical examination revealed nothing significant. It proved possible to eliminate insulin rapidly and to increase the diet to 75 Gm. of protein, 200 Gm. of fat and 150 Gm. of carbohydrate.

TABLE 7.—*Diet and Results of Urinalysis*

	Diet			Benedict's Test of Urine				Insulin		
Date	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	A.M. 7-11	P.M. 11-7	P.M. 4-9	A.M. 9-7	A.M.	Noon	P.M.
November 13....	60	150	100	+	+	4+	Complete reduction	..	10	10
November 19....	75	175	100	0	0	0	0	10	0	0
November 24....	75	200	125	0	0	0	0	0	10	0

A tolerance test was made on April 30.

Blood sugar estimations during fasting were: April 16, 129 mg.; April 22, 123 mg.; April 26, 123 mg.

He was discharged from the hospital on May 4.

He continued aglycosuric without insulin for six months. At the end of this time, following a cold, he had to resume the ingestion of 15 units of insulin before breakfast and 10 before supper.

CASE 22.—A man, aged 30, was admitted to the hospital on Oct. 26, 1925, three months after he had noticed increasing weakness and frequent headaches. About October 12, polyuria and polydipsia developed. During three months, he lost 20 pounds (9 Kg.).

On admission, physical examination was essentially negative except for evidences of wasting and dehydration. The blood sugar during fasting was 172 mg. per hundred cubic centimeters.

The diabetes was easily controlled with diet and insulin, and he was discharged on Nov. 11, aglycosuric, on a diet of protein, 60 Gm.; fat, 200 Gm., and carbohydrate, 150 Gm., with 20 units of insulin daily before breakfast.

He did not adhere to treatment and was readmitted on Sept. 17, 1927, on the verge of coma. On this occasion, signs of pulmonary tuberculosis were discovered, and bacilli were found in the sputum.

The results of tolerance tests made on Oct. 27 and Nov. 3 and 10, 1925, are shown in table 1.

Case 23.—A woman, aged 40, was admitted to the hospital on Dec. 1, 1927, one year after the development of intense genital pruritus. No glycosuria was found at that time. The pruritus was attended by frequency of urination and was not relieved by vaginal douches.

Physical examination revealed lacerations of the perineum. On admission, the urine showed a doubtful (±) reaction to Benedict's reagent. On a diet of 60 Gm. of protein, 150 Gm. of fat and 150 Gm. of carbohydrate the urine showed a complete reduction of Benedict's on one occasion after breakfast; other samples of urine contained smaller amounts of sugar.

A tolerance test was made on December 6.

She was discharged on December 9.

Case 24.—A woman, aged 42, was admitted to the hospital on Nov. 14, 1927. Glycosuria had been discovered in 1918; however, no diabetic symptoms appeared, although no restriction of the diet was practiced. In March, 1926, a blister appeared on the right great toe, which did not heal until June. On Nov. 11, 1927, she developed an infection of the right foot.

On admission, she presented a cellulitis of the right foot extending from an initial focus between the fourth and fifth toes. At the time of admission, the blood sugar during fasting was 170 mg. per hundred cubic centimeters. The infection cleared rapidly, and the foot healed with nonoperative, conservative treatment.

At first, 10 units of insulin was required with a diet of 70 Gm. of protein, 125 Gm. of fat and 100 Gm. of carbohydrate. Later, the use of insulin was eliminated, and the dosage of carbohydrate was increased to 125 Gm.

A tolerance test was made on November 28.

She was discharged on November 29.

Case 25.—A man, aged 25, admitted to the hospital on June 4, 1927, presented a typical picture of Friedreich's ataxia, which had developed in the course of the preceding five years. Three weeks before admission, polyuria and polydipsia appeared, and for a somewhat longer time he had been losing weight.

Except for wasting and the evidences of the Friedreich's ataxia, physical examination was essentially negative.

He proved to have a severe case of diabetes, and considerable difficulty was experienced in adjusting the dosage of insulin. After being discharged on July 30, he improved rapidly until September, at which time he was aglycosuric on a diet of protein, 60 Gm., fat, 200 Gm., and carbohydrate, 150 Gm., with 40 units of insulin before breakfast and 5 units before supper.

He was readmitted on Nov. 5, 1927, in coma from carbon monoxide poisoning and remained in the hospital five days. On a diet of 60 Gm. of protein, 200 Gm. of fat and 125 Gm. of carbohydrate he showed only traces of sugar in the urine at intervals, with 40 units of insulin before breakfast and 5 units before supper.

The results of a tolerance test, made on Nov. 9, 1927, are shown in table 1.

Case 26.—A woman, aged 56, was admitted to the hospital at intervals, beginning in May, 1923. Glycosuria and diabetic symptoms were first noted in 1922. At the time of her first admission, she had slight hypertension, general arteriosclerosis and evidences of early senile dementia. The diabetes was mild, responding to moderate dietary restriction alone. Owing to her mental condition, however, it was impossible to control the glycosuria at home, and her family sent her to the hospital at intervals when her symptoms became distressing. On these occasions, insulin was used temporarily to eliminate glycosuria.

The results of a tolerance test, made on Oct. 15, 1925, are shown in table 1.

On April 11, 1926, she suddenly became drowsy and weak, and weakness of the right side of the face and of the right hand developed; on April 24, a complete

right hemiplegia developed, later complicated by bronchopneumonia. For a time, she required 45 units of insulin daily. As she improved, however, it was possible to reduce the dose to 10 units daily.

CASE 27.—A man, aged 39, admitted to the hospital on Nov. 20, 1927, had been troubled with polyuria for some years. Glycosuria had been discovered ten years earlier. On Nov. 1, 1927, he hit the right ankle against a box. It became red, tender, painful and swollen. On November 6, similar swellings appeared in both thighs. On admission he presented a deep cellulitis of the right foot and ankle and two abscesses in the thighs. These were drained on November 21. On Nov. 27, further incision of the ankle was necessary because the infection had involved the ankle joint and the adjoining bones. On December 6, pus was found in the urine. He gradually improved in spite of all these conditions until Feb. 28, 1928, when the temperature suddenly rose and signs appeared in the lungs. He died on March 5. Blood cultures were repeatedly taken and always proved negative, although *Staphylococcus aureus* in pure culture was obtained from all the abscesses and from the urine.

The diabetes, under the influence of infections, proved to be severe.

The results of a tolerance test, made on Nov. 23, 1927, are shown in table 1. On this day he received a diet of protein, 70 Gm., fat, 150 Gm., and carbohydrate, 132 Gm., with 45 units of insulin before breakfast, 20 before lunch, 40 before supper and 35 late in the evening. Nevertheless, all samples of urine throughout the twenty-four hours gave heavy reductions of Benedict's solution and moderate reactions for acetone. On the preceding and subsequent days, glycosuria was less marked when less insulin was given.

CASE 28.—A woman, aged 64, was admitted to the hospital on Oct. 16, 1924. A year earlier, because of polyuria and polydipsia she had consulted a physician who found glycosuria. She was placed on a diet and remained aglycosuric for six months. For four days before admission, the bowels did not move in spite of the administration of cathartics. At the time of admission, she appeared weak, emaciated and somewhat dehydrated. She had severe hemorrhoids and a rectum full of impacted feces. After the latter had been cleared out she was greatly relieved. She was discharged, aglycosuric, on a diet of: protein, 50 Gm.; fat, 200 Gm., and carbohydrate, 100 Gm., with 15 units of insulin daily before breakfast.

She was readmitted on Sept. 13, 1927, with moderate acidosis, as the result of a seriously infected hand. This condition finally healed under treatment, and she was discharged on November 22, aglycosuric, on a diet of protein, 70 Gm., fat, 200 Gm. and carbohydrate, 150 Gm., with 30 units of insulin before breakfast and 10 before supper.

The results of a tolerance test, made on Nov. 8, 1927, are shown in table 1. At this time she was receiving a diet of: protein, 70 Gm., fat, 300 Gm. and carbohydrate, 300 Gm., with 50 units of insulin before breakfast and 20 units before supper, and was constantly aglycosuric.

CASE 29.—A woman, aged 52, was admitted to the hospital on Nov. 9, 1927. Six weeks earlier coryza had developed associated with slight infrascapular pain. Three weeks later, she had a similar cold attended by fever, cough and night sweats. She had no diabetic symptoms. On admission, she was found to have slight hypertension, and an acute pharyngitis due to hemolytic streptococci. Glycosuria was discovered.

She was discharged, aglycosuric, on a diet of 70 Gm. of protein, 125 Gm. of fat and 100 Gm. of carbohydrate, with 30 units of insulin daily before breakfast.

After this, she was able to reduce the amount of insulin gradually to 16 units daily, by November.

The results of a tolerance test, made on November 11, are shown in table 1.

She was discharged on November 13.

Case 30.—A woman, aged 60, was admitted to the hospital on Nov. 16, 1927, and died on November 30. Permission for an autopsy was not obtained. Fifteen months earlier, she fell from a street car, sustaining an injury to the left shoulder which confined her to bed for three months and left a permanent disability. Glycosuria was discovered three months later, and was only partly eliminated by moderate dietary restriction. She also had polyuria and polydipsia, which persisted in spite of treatment. On November 11, she became drowsy and sleepy, and complained of dizziness, dyspnea and precordial pain on slight exertion.

At the time of admission, she appeared drowsy but irritable and not seriously ill, and she presented no abnormalities that could not be explained as the result of age and moderate arteriosclerosis. She complained of general pains and was unmanageable, at times refusing to eat. Her mental state was somewhat better from November 18 to 25, when she relapsed into her previous condition and refused all food. At the same time tachycardia developed. On November 29, she suddenly became stuporous and lost the use of the right arm and leg. She also became incontinent of urine and feces. That evening she lapsed into coma. The next day, signs of pneumonia appeared in the lungs, the temperature rose rapidly and she died.

The results of a tolerance test, made on November 23, are given in table 1. At this time, she was receiving a diet of: protein, 70 Gm.; fat, 150 Gm., and carbohydrate, 100 Gm., with 20 units of insulin before breakfast and 15 units before supper.

On November 21, the blood sugar during fasting was 340 mg. per hundred cubic centimeters.

Case 31.—A woman, aged 49, admitted to the hospital on Sept. 9, 1927, had noticed increasing fatigability and sleeplessnes for two years. For three months, she had been troubled with dysuria and genital pruritus, and later with nocturnal and diurnal urinary frequency and axillary and submammary pruritus.

On admission, she appeared obese and presented an erythematous intertrigo in the axillae, under the breasts and about the genitalia; varicose veins of the legs, and slight edema of the ankles. The rash and itching disappeared rapidly under local and diabetic treatment. On admission, the blood sugar during fasting was 259 mg. per hundred cubic centimeters, and 20 units of insulin was required to prevent glycosuria, with a diet of 60 Gm. of protein, 100 Gm. of fat and 100 Gm. of carbohydrate. When she left the hospital, on Sept. 23, only 5 units was needed to keep her aglycosuric, with a diet of protein, 70 Gm.; fat, 75 Gm., and carbohydrate, 120 Gm. On November 21, the blood sugar during fasting was 192 mg.

The results of a tolerance test, made on November 15, are shown in table 1. On this day, the urine was sugar-free, and she was on a diet of: protein, 52 Gm.; fat, 95 Gm., and carbohydrate, 100 Gm., with 15 units of insulin before breakfast.

AURICULAR FIBRILLATION

RESULTS OF SEVEN YEARS' EXPERIENCE WITH QUINIDINE SULPHATE THERAPY (1921 TO 1928)*

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During the ten years following the introduction of quinidine [1] for the restoration of normal rhythm in cases of auricular fibrillation, ample opportunity has been afforded for the clinical and experimental study of this drug. To date more than 1,000 cases of permanent auricular fibrillation in which this treatment was used have been reported in the literature.[2] There can no longer be any doubt concerning the efficacy of quinidine in certain cases of absolute arrhythmia; its value in such cases justifies its continued use. We herein report a follow-up study of a series presented by one of us (P. D. W.) five years ago,[3] and we also present a new series of cases collected since that time.

OLD SERIES (1923)

In 1923, Viko, Marvin and White [3] reported seventy-one cases of nonparoxysmal auricular fibrillation and four cases of auricular flutter from the Massachusetts General Hospital and the New Haven Hospital: in 68 per cent of these patients the rhythm was restored to normal by quinidine, but in only 34 per cent was it maintained during the period of observation which varied from a few days (in the last case) to more than ten months. We present here the data obtained from a follow-up study of these patients. Three patients died apparently as a result of the quinidine therapy. To the present time (August, 1928) at least twenty-two more patients have died, but not from the quinidine therapy; so that at least one third of the entire group has died. Normal rhythm had been restored in sixteen of these twenty-two patients; in six the duration of normal rhythm was only from a few hours to days, so that quinidine therapy was undoubtedly without influence on the final outcome. Three of these six patients died of infec-

* Submitted for publication, Oct. 24, 1928.

* From the Massachusetts General Hospital.

1. Frey, W.: Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, Berl. klin. Wchnschr. **55**:450, 1918.

2. Eismayer, G.: Die Behandlung Unregelmässiger Herztätigkeit mit Chinidin, Deutsches Arch. f. klin. Med. **156**:182, 1927.

3. Viko, L. E.; Marvin, H. M., and White, P. D.: A Clinical Report on the Use of Quinidine Sulphate, Arch. Int. Med. **31**:345 (March) 1923.

tions (miliary tuberculosis, bronchopneumonia and a streptococcus infection); one patient died from congestive failure a number of days after the course of quinidine therapy; one died two months later and one died five and a half years later. In three of the remaining ten patients the duration of normal rhythm was unknown; one of these died from bronchopneumonia and cardiac failure, eight months after quinidine therapy was used, one died three years later from heart disease and one died four years later. One patient who maintained normal rhythm for six and a half months died six and a half years later; one patient maintained normal rhythm for more than four months and died suddenly four years later, and two other patients, who maintained normal rhythm for thirteen and eleven months, respectively, died four years and two years later, respectively. Thus only three of the patients who died maintained normal rhythm until the time of death, the duration in these cases being six months, one and a half years (death from congestive failure) and three years (death from probable coronary thrombosis), respectively.

In the group in which normal rhythm was not restored, the duration of life after quinidine therapy for the remaining six patients who died was two months in two patients, three months in one, five and a half years in one and an unknown period in two.

We have been able to obtain follow-up data on thirteen other patients, all of whom are living, so that our observations are complete in thirty-eight cases, or over half of the entire series. Two patients have had uninterrupted normal rhythm for six and seven years, respectively; a third patient has had normal rhythm for six years, interrupted by one short paroxysm of auricular fibrillation; a fourth patient, after six years of normal rhythm, had a relapse of auricular fibrillation uninfluenced by quinidine therapy; a fifth patient, who was observed for only three years, maintained normal rhythm except for one or two readily controlled paroxysms, and a sixth patient, who has maintained normal rhythm for seven years, has a daily paroxysm of auricular flutter (?). The last mentioned patient prefers a paroxysmal to a constant arrhythmia. Thus, normal rhythm has persisted for from six to seven years (for three years in one patient who was then lost track of) in 11.7 per cent of the patients who responded to quinidine therapy, or in 23.1 per cent of those who did not have a relapse within the first ten months after the restoration of normal rhythm. It may be said, therefore, that in a small, but not insignificant group, the restoration of normal rhythm by means of quinidine sulphate is permanent (to date). We have observed two other patients, not included in this or the present report, who have maintained normal rhythm from the time it was restored until death, two and four years later, respectively.

Two of the seven remaining patients, five of whom had normal rhythm for a number of hours or days, are distinctly limited in their activity as a result of heart disease, and the remaining five are in fair health, though they are not symptomless and are living a restricted life.

The health of the group of patients who maintained normal rhythm is definitely better than that of the group in which normal rhythm was not restored or in which auricular fibrillation recurred within a short time. Five patients, including two patients who did not belong to this series, maintained normal rhythm until death, the duration of life being six months, one and a half years, two years, three years and four years, respectively. The duration of life in six unsuccessfully treated patients was two months in two patients, three months in one, five and a half years in one and an unknown period in two. Four other patients in whom normal rhythm was maintained for four months, six and a half months, eleven months and thirteen months, respectively, lived for four, six and a half, two and four years, respectively. Six patients in whom normal rhythm lasted only a few hours or days died soon after the quinidine therapy. Duration of life is therefore definitely longer in patients who maintain normal rhythm for six months or longer than in those who quickly revert to fibrillation or do not attain a normal rhythm. There is, however, no clear indication that life is prolonged by the resumption and maintenance of normal rhythm.

NEW SERIES OF CASES (1923-1928)

The new cases of nonparoxysmal auricular fibrillation and auricular flutter reported in this paper were seen at the Massachusetts General Hospital and in private practice during the past five years. This group consists of patients seen since the first report was made, and therefore is composed of new patients, with the exception of one or two who reentered the hospital on account of a relapse of auricular fibrillation. The total number of seventy cases comprises sixty-two of fibrillation and eight of flutter. Of the sixty-two patients with auricular fibrillation who were treated with quinidine sulphate, normal rhythm was restored in forty-two, or 67.7 per cent; of the eight cases of flutter, four patients, or 50 per cent, were successfully treated. Of the entire group, therefore, circus movement was abolished in forty-six, or 65.7 per cent, in comparison with 68 per cent of seventy-five cases reported in 1923 from the Massachusetts General Hospital and the New Haven Hospital,[3] and with 58.5 per cent of 1,058 cases collected by Eismayer in 1927.[2]

To date seventeen patients, or 24.3 per cent of the entire series of new cases, have died; eleven of these had had normal rhythm restored. Slightly less than one fourth, therefore, of the patients successfully treated with quinidine sulphate have already died. One patient died from bronchopneumonia shortly after the restoration of normal rhythm;

one died during the course of quinidine therapy shortly after the recurrence of auricular fibrillation; one from congestive failure soon after the restoration of normal rhythm; one during an unsuccessful course of quinidine therapy after two successful courses, and one following an operation, six days after the recurrence of auricular fibrillation. Four other patients died one month, seven months, eight months and one year, respectively, after the resumption of normal rhythm, but the duration of the normal rhythm is unknown. The tenth patient maintained normal rhythm for three years, when auricular fibrillation recurred at about the time of onset of subacute bacterial endocarditis. The duration of life in the eleventh patient is unknown.

In four of the six patients in whom normal rhythm had not been restored before death, the duration of life after the course of quinidine therapy was seven months, eight months, eleven months and two years, respectively; two patients died while still in the hospital.

Death occurred in 23.8 per cent of the patients in whom normal rhythm was restored and in 23.1 per cent of those in whom normal rhythm was not restored.

Thirty-five patients in whom normal rhythm was restored are living. Auricular fibrillation recurred in four patients from a few hours to one or two weeks. Four patients left the hospital with a normal rhythm, but have not been seen again. Six patients maintained normal rhythm for one month, five months, six months, eight months, fourteen months and four years, respectively, before experiencing a recurrence of the auricular fibrillation. In the remaining twenty-one patients, normal rhythm was maintained until the time of the last examination; that is, for four months or less in five patients, and in the remaining patients, for five months, eight months, ten months (two patients), eleven months, thirteen months, twenty-one months, twenty-two months, two years (in three patients), three years, three and a half years, and four years (two patients), respectively. The health of the patients in this group as a whole is good. One patient is troubled considerably by paroxysmal auricular fibrillation; another patient has paroxysms from two to three times a year, readily controlled by quinidine, and a third patient suffered from paroxysms for the first two and a half years after the restoration of normal rhythm, but for the past year and a half has been free from attacks.

Twenty-four cases in this series have been classed as failures, but in two of these the patients had previously had a restoration of normal rhythm while under treatment with quinidine, while a third patient was subsequently successfully treated and has now maintained a normal heart rhythm for five years interrupted by occasional short attacks of auricular fibrillation. One patient, in spite of unsuccessful quinidine and digitalis therapy, reverted spontaneously to normal rhythm five

years after the onset of auricular flutter. Follow-up data have been obtained in six of the remaining fifteen patients in this group who are living. Two were fairly well from two to three months later; one patient wrote that she had been in poor health for two and a half years, but that after an operation for gastric ulcer she was much better; one patient, a year and a half after discharge from the hospital, wrote that he was in poor health; a fifth patient is in good health two years later, although troubled by gallstones, and the sixth patient is in fair health one and a half years after leaving the hospital.

One of the patients who temporarily regained a normal heart rhythm is in good health, four and a half years later, and one has required institutional care since leaving the hospital two years ago.

During a period of observation of four years in the oldest cases, a normal rhythm has been maintained in 30 per cent of the entire series. This result is actually much better than that obtained in the original series, for although 34 per cent of the patients maintained normal rhythm at the time that the report was made, the oldest cases were observed during a period of only ten months. Our follow-up studies indicate definitely that much more satisfactory results have been obtained in the present series. The evidence in both series indicates that the health of the patients successfully treated is better than that of those unsuccessfully treated, but that there is no essential difference in mortality or in duration of life.

The criteria used in the selection of cases for quinidine therapy were: safety, the probability of success and the likelihood of benefiting the patient by terminating the abnormal rhythm. Patients with marked mitral stenosis or with congestive failure not readily responding to rest and digitalis were excluded. Quinidine therapy was not used in a number of suitable cases, as it was felt that the patient had nothing to gain by converting fibrillation to a normal rhythm. With the exception of two or three cases in which it was hoped that restoration of normal rhythm might avert a fatal outcome the condition of each patient was satisfactory when quinidine therapy was begun. Most of the patients were completely digitalized as a preliminary measure, even though there was no congestive failure. The usual though not invariable routine, after the customary test doses were given, was to administer 6 grains (0.38 Gm.) every two hours, five times a day, until normal rhythm was restored or toxic symptoms occurred. If this procedure was unsuccessful after from five to seven days, the drug was discontinued. All the patients received daily rations of from 3 to 9 grains (0.19 to 0.58 Gm.) after the restoration of normal rhythm for as long a time as they remained in the hospital. They were instructed to continue taking the drug at home for a few weeks and then, if possible, to get on without it.

That large doses of quinidine may usually be administered with impunity, even to patients with grave conditions of the heart, cannot be denied.[4] It is equally certain that quinidine is a powerful drug, and that undesirable and even fatal events may occur from its toxic action, apart from the results of embolism. It is reasonable to assert, therefore, that large doses should be avoided if possible. If patients are properly selected for treatment, success is usually attained with surprisingly small amounts of the drug. Nor is proper selection of cases alone necessary. On the basis of clinical observations it appears that predigitalization, contrary to the opinion of some writers, allows the termination of circus movement with smaller doses of quinidine than would otherwise be required. It has been noted, in reviewing the literature, that the method occasionally or frequently practiced in administering quinidine is not the most efficient. The electrocardiographic [5] and pharmacologic evidence [6] available clearly indicates that the drug should be administered at least every two hours to obtain the best results.

In the present group, in which the percentage of successfully treated patients compares favorably with all the published series, thirty-six patients received less than 100 grains (6.48 Gm.) of quinidine, and only eight required more than 100 grains of the drug before the abnormal rhythm was terminated. In two cases, the amount of quinidine taken is not known. In twenty-eight patients, 50 grains (3.24 Gm.) or less of quinidine was all that was needed to restore normal rhythm.

The number of days of treatment with quinidine in the successful group was three or less in thirty-three cases, two in nineteen cases, one in five cases and more than seven in only two patients.

FACTORS INFLUENCING THE RESPONSE TO QUINIDINE THERAPY

Sex.—The group includes forty male patients in whom normal rhythm was restored in twenty-eight or 70 per cent, and thirty females, of whom 60 per cent were successfully treated. It seems unlikely that sex is of any importance in determining or influencing the outcome of treatment, in spite of the disparity of the two groups.

Age.—In studying the distribution of successes and failures according to age, it was found impracticable to divide the cases into decades,

4. Levine, S. A., and Stevens, W. B.: The Therapeutic Value of Quinidin Sulphate in Coronary Thrombosis Complicated by Ventricular Tachycardia, Am. Heart J. **3**:253, 1928. Sidel, N., and Dorwart, F. G.: Quinidin Sulphate in Auricular Fibrillation, Boston M. & S. J. **196**:216, 1927.

5. Lewis, T.; Wedd, A. M.; Drury, A. N., and Iliescu, C. C.: Observations upon the Action of Certain Drugs upon Fibrillation of the Auricles, Heart **9**:207, 1922.

6. Weiss, S., and Thatcher, R. A.: Studies on Quinidin, J. Pharmacol. & Exper. Therap. **30**:335, 1927.

as this resulted in groups too small to be of any value. We, therefore, made the division into two groups, one comprising all the patients from 10 to 40 years of age, and the other all the patients from 41 to 70 years of age. (A more detailed analysis of the factor of age has been made without, however, altering the conclusions.) In the group of younger patients (twenty-two), 81.8 per cent were treated successfully whereas in the group of older patients (forty-eight), normal rhythm was restored in only 58.3 per cent. This difference is striking and will be discussed in greater detail subsequently.

Congestive Failure.—It has been stated by others that congestive failure influences adversely the result of treatment with quinidine sulphate and may be responsible for the variety of responses seen in the different age or etiologic groups. To exclude this factor, it is an easy matter to revise our figures by removing from the two large age

TABLE 1.—*The Entire Series of Cases Divided Into Etiologic Groups*

Etiology	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Rheumatic	16	8	66.7
Hypertensive	3	0	100
Arteriosclerotic	10	6	62.5
Hypertensive and arteriosclerotic	3	6	33.3
Hypertensive and rheumatic	1	0	100
Hyperthyroid	3	2	60
Hyperthyroid and rheumatic	1	0	100
"Normal"	7	0	100
Doubtful etiology	2	2	50
Total	46	24	65.7

groups the twenty-three cases in which the condition was complicated by the presence of congestive failure at the time of admission to the hospital. Then there are fifteen cases in the younger group with restoration of normal rhythm in 93.3 per cent, and thirty-two cases in the older group, with restoration of normal rhythm in 65.6 per cent. Using these figures as a criterion, it is doubtful whether congestive failure influences the distribution of failures and successes in the various age groups to any important degree, although it may be a slight factor.

Etiology.—Table 1 shows the division of the entire series into the various etiologic groups, together with the number of cases in each group and the results obtained.

It seems reasonable, for the purpose of statistical study, to combine the second, third and fourth groups in table 1 under the one etiologic heading, "hypertensive and arteriosclerotic," and to exclude the four cases of doubtful etiology, the case of a hypertensive and rheumatic heart and the case of a hyperthyroid condition and a rheumatic heart.

Table 2 shows this revision and also the result of simplifying still further the two largest etiologic groups by removing the factor of congestive failure; the data for all patients who presented evidence of this complication were excluded in the second half of the table.

It is of interest to consider the possible influence of age on the outcome of treatment in each etiologic group. Table 3 has been constructed with this end in view.

TABLE 2.—*Revised Classification of Cases into Etiologic Groups* *

Etiology	Entire Series			Restricted Series		
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Rheumatic	16	8	66.7	11	5	68.8
Hypertensive and arteriosclerotic	16	12	57.1	12	5	70.6
Hyperthyroid	3	2	60			
Normal	7	0	100			

* The four cases of doubtful etiology, the one in which there was a hypertensive and rheumatic condition of the heart and the one in which there was hyperthyroidism and a rheumatic condition of the heart have been excluded. In the restricted series in this and the following table, the cases in which there was congestive failure have been excluded.

TABLE 3.—*Etiologic Groups Divided According to the Age of the Patients*

Etiologic Group	Entire Series						Restricted Series					
	Ages from 10 to 40 Years			Ages from 41 to 70 Years			Ages from 10 to 40 Years			Ages from 41 to 70 Years		
	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Rheumatic	12	3	80	4	5	44.4	9	1	90	3	3	50.0
Hypertensive and arteriosclerotic	1	0	100	15	12	55.5	1	0	100	11	5	68.7
Hyperthyroid	0	0	...	3	2	60						
Normal	4	0	100	3	0	100						

Tables 1, 2 and 3 indicate a significant variation in response to quinidine therapy in the different age and etiologic groups. The exact rôle played by etiology and age cannot, however, be conclusively demonstrated from these figures alone. On account of the natural distribution of the diseases under discussion, the younger group contains most of the cases of rheumatic heart disease, while the older group contains all but one of the cases of a hypertensive and arteriosclerotic condition of the heart. Table 3 indicates that age is of importance in the group

with rheumatic heart disease, but table 4, so far as one may draw conclusions from small groups, affords little or no evidence that age is a significant factor in this etiologic group. It becomes apparent that the striking difference between the two age groups in the response to quinidine therapy is related to the presence in the younger group of almost two thirds of all the cases of rheumatic heart disease, comprising over 68 per cent of the younger group. It is possible that age, so far as it has a bearing on the duration of heart disease, may be a factor of importance only in the cases of rheumatic disease with mitral stenosis; that is, the duration of mitral obstruction may be directly related to the degree of auricular damage, the extent of which might hinder the restoration of normal rhythm.

TABLE 4.—*Cases of Hypertensive and Arteriosclerotic Heart Disease Grouped According to Age*

Years	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
30 to 40	1	0	100
41 to 50	3	2	60
51 to 60	6	5	55
61 to 70	6	5	55

TABLE 5.—*Classification of Cases as to Age and Duration of Fibrillation*

	Less Than One Month			More Than One Month		
Age Group	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
10 to 40	10	2	83.3	4	2	66.7
41 to 70	7	2	77.7	17	18	48.6

There is some evidence that etiology has a minor influence on the response to quinidine therapy. All the cases of hyperthyroidism were in patients more than 40 years of age, and the response in this group was essentially the same as in the group with hypertensive and arteriosclerotic heart disease. The possibility is suggested, therefore, that the poor results in these two groups and in the older group of patients with rheumatic disease of the heart may be due, not to the age factor, but to the associated vascular changes that may occur with advancing age. In a normal heart, uniformly good results are obtained, irrespective of the age of the patient and of the duration of the fibrillation.

In the following paragraphs, evidence is presented to show the important influence of the duration of fibrillation on the response to

quinidine therapy; it is shown that this influence is independent of age and etiology. To determine if the factor of the duration of fibrillation is responsible for the apparent influence of age and etiology we have constructed tables 5 and 6 (in table 5 the data for the seven patients with normal hearts have been excluded). The conclusions already reached regarding these two factors are corroborated by the data in these tables and in table 10; that is, the etiology is of minor importance, whereas age is an important factor in the rheumatic group.

Duration of Fibrillation.—The duration of fibrillation at the time that quinidine therapy is started appears to exert considerable influence

TABLE 6.—*Cases of Rheumatic Heart Disease, Classified as to Age and Duration of Fibrillation*

	Ages from 10 to 40 Years			Ages from 41 to 70 Years		
Duration of Fibrillation	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than one month	8	1	88.9	1	1	50
More than one month	4	2	66.7	3	4	42.8

TABLE 7.—*Entire Series of Cases Grouped According to the Duration of Fibrillation*

Duration of Fibrillation	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than one month	18	4	81.8
1 to 6 months	15	11	57.7
6 months to 1 year	5	4	55.5
1 to 2 years	3	2	60
2 to 3 years	0	2	0
3 to 4 years	1	0	100
5 to 10 years	1	1	50
Over 10 years	2	0	100
Questionable	1	0	100

on the outcome of treatment, as may be seen from tables 7 and 8. The patients with fibrillation of recent origin show the best response, as in 90 per cent of these the arrhythmia is terminated. In all cases of more than one month's duration, irrespective of the number of months or years of fibrillation, there is an equal propensity for normal rhythm to be restored when the patient is treated with quinidine; in some of our most strikingly successful cases, the patients had had auricular fibrillation for more than ten years.

We may conclude, then, that the duration of fibrillation is to a limited extent a decisive factor in the outcome of treatment. If the cases are divided into the two age groups already mentioned, it becomes

clear that age can be excluded as a factor in varying the response to treatment in any group formed on the basis of the duration of fibrillation.

The discrepancy seen in the cases with fibrillation of over six months' duration depends on the presence, in this group, of five of the seven patients with normal hearts, four of whom fall in the age group of from 10 to 40 years. In addition, of the failures in this group one patient was almost moribund when quinidine was first given, and three other patients received inadequate amounts of the drug.

If the group is still further analyzed to determine whether an etiologic factor may explain the variation in response apparently related

TABLE 8.—*Duration of Fibrillation in Patients with and without Congestive Failure*

	Entire Series			Restricted Series,
Duration of Fibrillation	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Percentage in Which Normal Rhythm Was Restored
Less than one month	18	4	81.8	93.3
More than one month	27	20	57.4	64.5

TABLE 9.—*Grouping of Cases as to Duration of Fibrillation and Age*

	Ages from 10 to 40 Years			Ages from 41 to 70 Years		
Duration of Fibrillation	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than 1 month	10	2	83.3	8	2	80
1 month to 6 months	2	2	50.0	11	9	55
6 months to 1 year	2	0	100.0	5	4	55.5
Over 1 year	4	0	100.0	3	5	37.5

to the duration of fibrillation, the results obtained are striking—although we are now dealing with small figures—and indicate that etiology may be excluded as a factor in estimating the influence of the duration of fibrillation on the response to quinidine therapy (table 10).

Condition of the Patient.—The condition of the patient, as estimated by the presence of objective signs of congestive failure, the general clinical impression and the ventricular rate when quinidine therapy is started (the latter, however, is closely related to digitalization), is of some importance in its influence on the success or failure of treatment. Of twenty-three patients presenting evidence of congestive failure on entrance to the hospital, normal rhythm was restored in only 47.8 per cent, while of forty-five patients without this complication, normal rhythm was restored in 73.3 per cent. However, nine of the eleven patients in whom normal rhythm was restored had marked

failure, while only five of the twelve whose rhythm was not restored to normal presented evidence of considerable failure. In this group of patients with congestive failure, in only 57.1 per cent of the seven cases with fibrillation of less than one month's duration was rhythm restored to normal; of the sixteen with fibrillation of over one month's duration, rhythm was restored to normal in 77.7 per cent.

Three of the eleven patients of this group in whom quinidine terminated circus movement died, one following an operation, one from progressive congestive failure (normal rhythm was maintained to the end) and one from bronchopneumonia. Quinidine can be definitely excluded as a cause of death in these cases.

One of the twelve patients in whom normal rhythm was not restored died from pneumonia and one died from congestive failure.

In this entire group of twenty-three patients with congestive failure, with the exception of two patients who died, the condition of the patients,

TABLE 10.—*Grouping of Cases According to Duration of Fibrillation and Etiology*

	Rheumatic			Hypertensive and Arteriosclerotic		
Duration of Fibrillation	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than one month	9	2	81.8	5	1	83.3
Over one month	7	6	53.8	11	11	50

as the result of rest and digitalization, was satisfactory when quinidine therapy was started.

Size of the Heart.—In ten patients without any cardiac enlargement the rhythm was restored to normal in all, this group including, of course, the seven patients with apparently normal hearts. The rhythm was restored to normal in forty patients, 57.5 per cent, with from slight to moderate enlargement, and in nineteen patients, 63.1 per cent, with marked enlargement. The relative size of the heart when it is enlarged, therefore, seems to bear no relation to response to quinidine therapy.

A past history of decompensation and the type of fibrillation as seen in the electrocardiogram (fine or coarse) have no influence on the outcome of treatment. Rhythm was restored to normal in 67.8 per cent of twenty-eight patients whose electrocardiograms showed the fine type of fibrillation, while it was restored to normal in 71.4 per cent of twenty-eight patients with a coarse type of fibrillation.

Ventricular Rate.—The ventricular rate when quinidine is started is apparently of some importance as may be seen from table 11. The ventricular rate, however, is largely influenced by digitalization in these

cases; the figures in tables 12 and 13 suggest the beneficial action of digitalization in favoring the response to quinidine. Three patients received no digitalis while in the hospital, but the nature of the T wave of the electrocardiogram indicated probable digitalization before entrance. The data for these cases are not included in the table.

In sudying the effect of digitalis on the rate of circus movement, Lewis [5] and his co-workers found that constant results were obtained only when the drug was given in full therapeutic doses. The only patient in whom a fall in rate of circus movement was observed was

TABLE 11.—*Cases Grouped According to Ventricular Rate When Quinidine Therapy Began*

Ventricular Rate	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Less than 80	25	11	69.4
80 to 90	5	5	50
90 to 100	2	4	33.3
More than 100	4	4	50

TABLE 12.—*Cases Grouped According to the Degree of Digitalization*

Digitalization	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Complete	36	18	66.7
Insufficient	2	3	40
None	5	3	62.5

TABLE 13.—*Cases Grouped According to Degree of Digitalization*

Digitalization	Normal Rhythm Restored	Normal Rhythm Not Restored	Percentage in Which Normal Rhythm Was Restored
Complete	36	18	66.7
None or insufficient	7	6	53.8

receiving only small doses of digitalis. We have, therefore, in table 13, combined the two groups: those in which the patients received no digitalis and those in which an insufficient amount was given. It is evident that the response is better in patients who have been fully digitalized.

Miscellaneous Factors.—In studying the cases we have attempted, in each instance, to explain a failure. By doing so, we have been able in a large measure to account for many of the unsuccessful cases. Probable causes, at least, may be assigned, but one can never state with finality, on clinical grounds alone, the ultimate cause of failure. Such a

study has merely emphasized that certain conditions may interfere with the desired action of the drug.

The entire group of failures includes twenty-six cases of permanent fibrillation and flutter. It is interesting that in nine of these twenty-six cases the patients received strikingly small doses of quinidine, on account of the development of toxic symptoms, or because of refusal to accept the treatment as prescribed, or for no good reason at all. It is fair to assume that in at least a few of these patients, the fibrillation would have been converted to normal rhythm with adequate doses of quinidine. Four other patients had auricular flutter, and it has been our experience, as well as that of others, that quinidine is not so effective in this condition as is digitalis. Study of these four cases reveals additional possible reasons for the undesirable outcome. One patient entered with extreme congestive failure and hyperpyrexia, and soon died. This patient, furthermore, received only 36 grains (2.33 Gm.) of quinidine in two days. A second patient had severe heart disease with considerable enlargement and crippling angina pectoris. A third patient was given no digitalis. The case of the fourth patient is remarkable in that after five years of persistent flutter, the paroxysm ended spontaneously.[7] Two patients with auricular fibrillation were inveterate drinkers of alcoholic beverages; and since we have repeatedly observed that alcohol may apparently precipitate auricular fibrillation, we therefore suggest the possibility that this fact may have interfered with quinidine therapy. In addition, one of these patients received inadequate doses of quinidine. In three other patients, an intercurrent infection complicated the situation; in one patient, a severe, fatal pneumonia. Two of these three patients were in poor condition when the quinidine therapy was started, and one patient was incompletely digitalized.

We may conclude, then, that in addition to factors already discussed, failure to restore normal rhythm in our series depended on inadequate amounts of quinidine, intercurrent infection and possibly alcoholism. As a rule, more than one factor was present in a given case, accentuating the probability of failure. Grossly inadequate dosage of quinidine was the most frequent cause, being present in more than one third of the failures.

THE USE OF DIGITALIS WITH QUINIDINE

The use of digitalis with quinidine in the treatment of patients with auricular fibrillation has not been sanctioned by all who have studied this problem. In the literature, the views expressed vary from a recom-

7. Sprague, H. B., and White, P. D.: Auricular Flutter, J. A. M. A. **90**:1772 (June 2) 1928.

mendation of its use to a declaration that it is contraindicated because of the combined toxic effects of the two drugs.

Cantani,[8] in a publication of 1905, is given credit for the opinion that quinidine exerts a favorable influence on the action of digitalis. Schott,[9] in 1920, advised against the combined administration of quinidine and digitalis, on the grounds that a high degree of A-V block was thus produced in guinea-pigs. In repeating these experiments, Korns [10] came to the conclusion that asphyxia, produced by the action of quinidine on the respiration, was responsible for these high grades of A-V block, and that if the precaution were taken to exclude this factor, one never observed a block of a higher grade than 2:1. According to Korns, asphyxia alone is capable of producing all grades of A-V block in guinea-pigs, including complete dissociation. Frey, in his second publication on the use of quinidine,[11] advocated digitalization in cases of congestive failure, but, in a later publication,[12] was of the opinion that the combined use of digitalis and quinidine was not advisable. In a previous publication [3] on the treatment of auricular fibrillation reported from the Massachusetts General Hospital, the authors advocated digitalization in those cases complicated by congestive failure. The successful action of quinidine in terminating arrhythmias in digitalized animals has been convincingly demonstrated in experiments recently reported by Haskell.[13]

In the present series of cases, most of the patients received digitalis prior to treatment with quinidine. The data already presented point to the favorable influence of previous digitalization on the restoration of normal rhythm by means of quinidine sulphate. At any rate, our observations do not bear out the contention of some authors that digitalis antagonizes the successful action of quinidine. In addition, many of the digitalized patients received the smallest doses of quinidine used in the entire series, with restoration of normal rhythm, corresponding to the earlier experience in this hospital. This view, again, is in disagreement with those observers who believe that previous digitalization

8. Cantani, quoted by Haskell, C. C.: The Influence of Quinidin on the Cardiac Irregularity Produced by Digitalis, J. Pharmacol. & Exper. Therap. **32**: 223, 1928.

9. Schott, E.: Zur Frage der Chinidintherapie, Deutsches Arch. f. klin. Med. **134**:208, 1920.

10. Korns, H. M.: An Experimental and Clinical Study of Quinidin Sulphate: I. Experimental, Arch. Int. Med. **31**:15 (Jan.) 1923.

11. Frey, W.: Weitere Erfahrungen mit Chinidin bei absoluter Herzunregelmässigkeit, Berl. klin. Wchnschr. **55**:849, 1918.

12. Frey, W.: Chinidin zur Bekämpfung der Absoluten Herzunregelmässigkeit (Vorhofflimmern), Deutsches Arch. f. klin. Med. **136**:70, 1921.

13. Haskell, C. C.: The Influence of Quinidin on the Cardiac Irregularity Produced by Digitalis, J. Pharmacol. & Exper. Therap. **32**:223, 1928.

necessitates the subsequent use of larger doses of quinidine. Furthermore, we have failed to observe any undesirable effects which could be attributed to the combined use of both drugs.

Our opinion, therefore, based on our observations and on experimental and theoretical considerations, is that previous digitalization is justified as a preliminary step in the treatment of all patients with auricular fibrillation by means of quinidine sulphate. Our experience has led us to believe that such preliminary treatment is an important factor in the successful use of quinidine in some cases, and that occasionally it may be the deciding factor between failure and success. That the treatment may be consummated with smaller doses of quinidine is a further advantage of considerable importance, since we have seen patients who were so sensitive to quinidine that 3 grains (0.19 Gm.) have caused toxic symptoms coincidentally with the restoration of normal rhythm. It would appear, from a study of our cases, that the best results are obtained when digitalis is administered in doses sufficient, at least, to bring about inversion of the T wave in leads 1 and 2 of the electrocardiogram.

In emphasizing the value of digitalis, and in stating that it should be used as a matter of routine in every patient, it is not our intention to convey the impression that it is indispensable in all cases, since this would be contrary to fact. Indeed, it may be properly argued, on theoretical grounds, that digitalization, prior to the administration of quinidine, may interfere with the successful action of the latter drug in a rare case. It is presumably on the basis of such considerations that some physicians oppose the use of digitalis in these cases. Actually, we have never seen a case in which failure to restore normal rhythm could be definitely attributed to the use of digitalis, although such a possibility must be conceded.

REPORT OF CASES

In studying the problem of digitalization in this connection, we have been much more impressed by the observation of individual cases than by the statistics of the entire series. The following case in our series is a good illustration of the value of preliminary digitalization.

CASE 1.—A patient who had had fibrillation for many years was given a course of quinidine treatment, comprising over 150 grains (9.72 Gm.) of quinidine sulphate in five days. Normal rhythm was not restored. Five years later his condition was entirely unchanged so far as could be determined by careful questioning, physical examination and electrocardiographic study. The fibrillation by this time had a duration of at least fifteen years. Before quinidine was given, the patient was completely digitalized, so that the T waves in leads 1 and 2 were inverted. In three days, a total dose of 108 grains (6.99 Gm.) of quinidine sulphate restored normal rhythm without any untoward incident.

The relation of digitalization to the dosage of quinidine is shown in case 2.

CASE 2.—F. J. M., a man, aged 43, had had auricular fibrillation constantly for nine weeks. Following complete digitalization he was given two test doses of quinidine sulphate, 3 grains (0.19 Gm.) each, in three hours. This was sufficient to restore normal rhythm. Two and one-half years later he awoke in the morning in a paroxysm of fibrillation, the first since normal rhythm had been restored. Without previous digitalization he was started on quinidine; 30 grains (1.94 Gm.), or five times the amount used two and one-half years earlier, had to be given before normal rhythm was restored. His condition was similar in every way to that during the earlier attack, except that the fibrillation was then of nine weeks' duration, and now had existed only a few hours when quinidine therapy was started.

In cases of auricular flutter the same beneficial action of digitalis may be observed, as illustrated by case 3.

CASE 3.—A patient had an auricular flutter of fifteen months' duration. He was given a total dose of 159 grains (10.30 Gm.) of quinidine in eight days, without the restoration of normal rhythm. He was then digitalized, and normal rhythm was restored by 72 grains (4.66 Gm.) of quinidine sulphate in two days. Digitalization did not produce fibrillation in this case, so that we consider the final result as due chiefly to quinidine and not to digitalis.

The factors controlling circus movement in the auricle are: (1) the length of the path traversed by the wave; (2) the duration of the refractory period at any one point, and (3) the speed at which the wave is conducted.[11] By closing the gap between the crest and the wake of the circulating wave, circus movement may be interrupted and normal rhythm restored. This may be accomplished by (1) increasing the refractory period sufficiently, the other factors remaining constant, or by (2) increasing the rate of circus movement, the other factors remaining constant. Practically, these effects are interrelated, and the actual situation is a complicated one, the final result in any given instance depending on the preponderance of one effect over the other.

One of the constant effects of quinidine is to decrease the rate of circus movement.[14] The most striking result of quinidine, according to Lewis and his co-workers, is the increase of the refractory period, often amounting to 50 per cent or more. Under these conditions

14. Cohn, A. E., and Levy, R. L.: Experiments with Quinidin on Conduction and on the Refractory Period in the Dog's Heart, Proc. Soc. Exper. Biol. & Med. **19**:174, 1921-1922. Drury, A. N., and Iliescu, C. C.: The Restoration of the Normal Cardiac Mechanism in Cases of Auricular Fibrillation by Means of Quinidin Sulphate, Brit. M. J. **2**:511, 1921. Lewis, T.; Drury, A. N.; Iliescu, C. C., and Wedd, A. M.: The Manner in Which Quinidin Sulphate Acts in Auricular Fibrillation, Brit. M. J. **2**:514, 1921.

normal rhythm is restored only in those cases in which the effect on the refractory period predominates over the effect on the rate of circus movement.

Digitalis, like quinidine, acts directly on the muscle of the heart, and indirectly by stimulation of the vagus nerve, the effects being in opposite directions. Because one effect predominates in some instances and the other in the remaining instances, it is impossible to predict the action of digitalis in a given case. The usual effect, however, according to Lewis,[15] is an increase in the rate of circus movement. The conversion of flutter to fibrillation by digitalis is probably explained in this way.

The administration of quinidine following digitalization reduces the rate of circus movement to the same extent that it does in the absence of digitalis. The final circus rate, however, is definitely higher when digitalis has been used, since the rate is thereby higher when quinidine is started. Assuming now that quinidine has lengthened the refractory period of auricular muscle as much as when digitalis has not been used, the possibility of closing the gap is improved under the combined effects of quinidine and digitalis. The smaller the gap between the crest and wake of the circulating wave, the easier it is to close. Furthermore, the combined use of the drugs may favor the predominance of effect on the refractory period over that on the rate of circus movement; this would be significant in view of the nice balance which ordinarily exists. Finally, it is possible that digitalis causes the wave to circulate in a shorter path, which accounts in part for the increased rate of circus movement. That this takes place when flutter is converted to fibrillation under the influence of digitalis can hardly be doubted; such a change, moreover, facilitates the ease with which the gap may be closed.

We may say then, that although digitalis produces an effect on the fibrillating auricle opposite to that produced by quinidine, theoretically the combined action of the two drugs may favor the termination of circus movement. We may expect, under such conditions, to succeed with smaller doses of quinidine, and this actually has been our experience.

Digitalization is of value in preventing ventricular tachycardia, which is a frequent annoying result of the reduction in the rate of circus movement. In patients with slight congestive failure or limitation of reserve, it is to be expected that digitalization will improve their general condition.

A possible, but unproved, effect of digitalization is the prevention of fixed flutter, which may result from quinidine therapy and which may be distressing and even fatal.

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15. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B. Hoeber, 1925.

UNTOWARD RESULTS FROM QUINIDINE THERAPY

A number of patients complained of the minor manifestations of cinchonism—ringing in the ears, slight deafness, fulness in the head, headache, flushing, dizziness, itching of the skin and diarrhea. One patient died suddenly, but in reviewing the circumstances, it seemed unlikely that her death was due to quinidine. The patient was a woman, aged 46, with hypertension, hypertensive heart disease and auricular fibrillation which had been paroxysmal for four years and constant for two months before quinidine was given. Normal rhythm was restored by 96 grains (6.22 Gm.) of quinidine taken during a period of five days, without any toxic effects from the drug. After twenty-four hours, auricular fibrillation recurred. When last seen, the patient apparently was in good condition, the pulse rate being 80 per minute and irregular. Twenty-five minutes later, while sitting on the bed pan, she died suddenly. Autopsy was not permitted.

As is usual, transitional auricular flutter was observed in several patients, in the course of a change from auricular fibrillation to normal rhythm, but in this series fixed flutter did not occur.

In one patient a regular ventricular rhythm at the rate of 70 per minute without evident P waves in any of the customary axial leads occurred after several doses of quinidine. In later electrocardiograms one P wave was evident. Quinidine had to be discontinued on account of symptoms of cinchonism, and auricular fibrillation shortly recurred. Two other cases with regular ventricular tachycardia without evident P waves occurring as a result of quinidine therapy have come under our observation. These three cases will form the subject of a separate communication. From observation of these cases we believe it likely that standstill of the whole heart may explain some of the reported fatalities during quinidine therapy which were hitherto unexplained.

COMMENT

In the series reported previously from the Massachusetts General and New Haven Hospitals,[3] the first sixty of the total of seventy-five patients were practically unselected. The cases studied for the present report were all selected, one of the considerations being the probability of success according to the generally accepted criteria. Yet in the first series, in 68 per cent of the cases the rhythm was restored to normal and in the second series, in only 65.7 per cent. Our attention is arrested by this comparison, and it is pertinent to inquire into the meaning of the failure of selection to raise the number of favorable responses.

Following the work of Lewis we may attribute the termination of "fibrillation by quinidine to a predominant influence upon the refractory period," and the failure of quinidine "to its balancing or predominating influence on conduction," the balance ordinarily being a nice one. In

practice this may mean that in any series of cases in which the patients are properly treated the number responding to quinidine therapy will vary within small limits. Korns,[16] from a clinical study of his cases, finds "support for the theory that the action of quinidine in abolishing circus movement is not conditioned by the type of cardiac lesion, degree of decompensation, duration of fibrillation, etc., but is essentially related to the pathologic physiology of the auricular muscle."

We can hardly overlook the fact, however, that various factors may have considerable influence, and perhaps all the more so because quinidine effects a nice balance, at least in experiment, as it changes the refractory period and conduction in auricular muscle. Moreover, there is a greater difference in the degree of success attained with quinidine in the numerous series of cases reported in the literature than can be explained entirely on the basis of proper or improper treatment. And finally, a study of our cases indicates to us that certain factors, already discussed, do have a bearing on the outcome of treatment.

In judging the value of quinidine in general or in any one particular case, the permanence of the result obtained by its successful use is the most important consideration. If the restored normal rhythm is to be but a transitional state between two periods of permanent auricular fibrillation, it is best not to resort to the use of quinidine in this condition. The patient cannot be benefited by such treatment, and he has been exposed to the toxic action of the drug and to the danger of embolism. It is from this point of view especially that the selection practiced in this series of cases has appeared to be successful, as may be seen by referring to the follow-up study presented; for in the second series the number of "permanent" restorations of normal rhythm is much greater than in the first series.

That quinidine is a valuable drug, and that it is desirable to continue its use in permanent auricular fibrillation, is clearly evident from the large number of cases that we have now been able to follow for a number of years after the restoration of normal rhythm. There can be no doubt that these patients have been benefited by the drug.

QUINIDINE THERAPY IN OTHER CONDITIONS

We have had an opportunity to observe the effect of quinidine in twenty-nine cases of paroxysmal auricular fibrillation and two of paroxysmal auricular flutter. Most of these patients have been observed for a long period of time, from seven to eight years in the oldest cases. In sixteen of the patients with fibrillation, quinidine was beneficial; in

16. Korns, H. M.: An Experimental and Clinical Study of Quinidin Sulphate: II. Clinical, Arch. Int. Med. **31**:36 (Jan.) 1923.

five patients quinidine was of no value; in three patients its action was doubtful; in one patient it appeared to be effective at first but later not only was it ineffective, but it appeared to aggravate a regular tachycardia which occurred in addition to the paroxysms of fibrillation; and in four patients the action of quinidine could not be determined, in two of these on account of sensitiveness to the drug. A patient in whom quinidine was ineffective for the paroxysms of fibrillation found the drug useful for paroxysms of ventricular tachycardia. One of the patients in whom the action of quinidine on the fibrillation was doubtful had frequent premature beats which were effectively controlled by the quinidine; digitalis proved effective in stopping the paroxysms of fibrillation in this patient. The beneficial effect of digitalis was seen in one other patient in whom quinidine appeared to be entirely ineffective.

The beneficial action of quinidine was manifested in five patients by the termination of the paroxysms of fibrillation; in three patients quinidine was useful in reducing the number of paroxysms, while in four patients the number of paroxysms was reduced and the attacks were shortened. In three patients the paroxysms of fibrillation did not recur after rations of quinidine had been taken for a short period of time.

While quinidine appeared to be of definite value in 64 per cent of the patients with paroxysmal auricular fibrillation in whom the action of the drug could be estimated, other measures of treatment were resorted to in these patients, and these undoubtedly had some influence on the outcome of treatment. Reassurance, regulation of diet, avoidance of fatigue, improvement of the general physical condition and other such measures have contributed to the success of treatment.

One patient with paroxysmal flutter found quinidine ineffective, although digitalis seemed to be of value. The second patient with paroxysmal flutter took 18 grains (1.16 Gm.) of quinidine daily with almost constant regularity for about seven years. Although he had a daily paroxysm of flutter, he felt worse when not taking quinidine. He had no toxic symptoms from the constant use of quinidine. Digitalis appeared to make him worse.

Quinidine was effective in a small group of patients with either paroxysmal tachycardia or premature beats. In one patient with paroxysmal tachycardia quinidine was beneficial at first but later became ineffective; then digitalis was found to be effective. In another patient, quinidine successfully stopped some attacks of tachycardia; in others it did not, although digitalis was effective. A third patient had paroxysmal auricular fibrillation and paroxysmal ventricular tachycardia. Quinidine was effective for the paroxysmal ventricular tachycardia, although it had no influence on the fibrillation.

SUMMARY AND CONCLUSIONS

This paper consists primarily in a clinical study of the action of quinidine sulphate in sixty-two cases of permanent auricular fibrillation, eight cases of permanent auricular flutter, twenty-nine cases of paroxysmal auricular fibrillation, two cases of paroxysmal auricular flutter, and a small group of cases with paroxysmal tachycardia and premature beats. A follow-up study of a series of seventy-five additional cases of permanent auricular fibrillation and flutter reported in 1923 is also presented. We have reached the following conclusions from a study of this material:

1. In the series of seventy cases, comprising sixty-two of permanent auricular fibrillation and eight of flutter, normal rhythm was restored in 65.7 per cent.

2. In apparently normal hearts (seven cases), permanent auricular fibrillation was terminated by quinidine in 100 per cent of the cases, irrespective of the age of the patient and the duration of the fibrillation. These patients are the most satisfactory to treat.

3. The next most responsive group is that of patients with rheumatic heart disease who are less than 41 years of age.

4. In the hyperthyroid group the response is somewhat better than in the group of patients with hypertensive and arteriosclerotic heart disease.

5. When not dealing with normal hearts the most important single factor which influences the outcome of the treatment is the duration of fibrillation. This is true in a limited sense only, for the response is surprisingly high when the fibrillation has lasted less than a month; beyond this, duration apparently is of little or no importance.

6. Age is important in the group of patients with rheumatic heart disease. The desired response occurs in a high percentage of the young patients, but occurs in a much smaller proportion of the patients more than 40 years of age.

7. Etiology has but a minor influence on the response to quinidine therapy.

8. Recent congestive failure reduces the probability of success from the use of quinidine; the duration of fibrillation has not accounted for the poor response in the cases with congestive failure.

9. Factors contributing to failure in some of our cases were insufficient quinidine dosage, intercurrent infections and possibly alcoholism.

10. A past history of congestive failure, the size of the heart when enlarged, the type of fibrillation and sex appear to be of no influence on the outcome of treatment. In each of the ten patients with normally sized hearts normal rhythm was restored.

11. The history of fibrillation for a great many years, in the absence of valvular disease and congestive failure, recent or present, is not a contraindication for quinidine therapy.

12. It seems highly desirable to digitalize all patients as a matter of routine before starting quinidine. Full therapeutic doses should be used. There is clinical, experimental and theoretical justification for this view. Digitalization is not indispensable in many cases, but in some it will spell the difference between failure and success. Often normal rhythm may be attained with smaller doses of quinidine if digitalization has been resorted to. It may add to the comfort of the patient, improve his condition and possibly prevent fixed flutter. No harm has been observed from the combined use of digitalis and quinidine.

13. In this new group of seventy patients there was one death which might possibly be attributed to quinidine, but probably was not due to it.

14. The most frequent change of mechanism noted in the electrocardiogram was flutter, but in no case was it fixed. In the entire series of patients receiving quinidine in the Massachusetts General Hospital there were two cases exhibiting probable auricular standstill. A third case was seen in a private patient. It seems likely that some of the fatalities reported during quinidine therapy may have resulted from the standstill of the whole heart.

15. Quinidine is of value in preventing and terminating paroxysmal auricular fibrillation, and is effective in some cases of paroxysmal tachycardia and premature beats.

16. In cases of auricular flutter, digitalis is probably more effective than quinidine. Digitalis appears to be more effective than quinidine in occasional cases of paroxysmal auricular fibrillation and paroxysmal tachycardia.

17. In judging the value of quinidine in permanent auricular fibrillation, the criterion of greatest importance is the permanence of the results obtained. Our follow-up studies have indicated that (1) restored normal rhythm is "permanent" in a significant number of patients, and (2) although there is no definite evidence that normal rhythm prolongs life or reduces mortality, it is clearly evident that it promotes the health of the patient.

THE EFFECT OF DIGITALIS ON THE ELECTROCARDIOGRAM

AN EXPERIMENTAL STUDY ON DOGS AND CATS *

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Considerable attention has been paid to the electrocardiographic changes, particularly of the T wave, following the administration of digitalis. Experiments performed on human beings and on animals have not given the same results in the hands of different observers. Pardee,[1] using normal persons and patients with heart disease, found that the T wave began to decrease in amplitude as early as from two to four hours after the administration of tincture of digitalis in doses of 1 minim (0.06 cc.) per pound of body weight. The maximum effect was seen in from six to seven hours, and the change lasted for about twenty-four hours. The same author stated later that similar effects were noted with much smaller doses; in fact, with from one sixth to one eighth of the dose previously mentioned. Pardee [2] considered a change in the T wave as a reliable sign not only of the beginning action but also of the absorption of digitalis, and suggests this as a criterion for the effect of digitalis and as a method of standardization. He [3] used this method in comparing the effect of digitalis when given by the oral, hypodermic and intravenous routes.

In 1915, Cohn, Fraser and Jamieson [4] described the depression of the T wave following the administration of digitalis. They observed that the change in the T wave preceded the appearance of nausea or changes in the rhythm or conduction time. In human beings, the depression of the T wave developed into a negative wave after a dosage of 1.2 Gm. of dried digitalis leaves. Similar results were obtained by Marvin, Pastor and Carmichael [5] in patients before an operation

* Submitted for publication, Nov. 30, 1928.

* From the Institute of General Experimental Pathology of the University of Vienna, Prof. C. J. Rothberger, Director.

1. Pardee, H. E. B.: Rate of Absorption of Digitalis from the Gastro-Intestinal Tract: Clinical Study, J. A. M. A. **75**:1258 (Nov. 6) 1920.

2. Pardee, H. E. B.: Standardization of Digitalis by Its Action on Human Heart, J. A. M. A. **81**:186 (July 21) 1923.

3. Pardee, H. E. B.: Hypodermic Digitalis Preparations, J. A. M. A. **85**: 1359 (Oct. 31) 1925.

4. Cohn, A. E.; Fraser, F. R., and Jamieson, R. A.: J. Exper. Med. **21**:593, 1915.

5. Marvin, H. M.; Pastor, R. B., and Carmichael, M.: Electrocardiogram and Blood Pressure During Surgical Operation and Convalescence, Arch. Int. Med. **35**:782 (June) 1925.

was performed. Harris [6] also reported such changes. Cohn and Stewart [7] reported that they found a change in the T wave constantly in dogs after intravenous injections of tincture of digitalis or digifoline. They gave digitan by mouth and also found a changed T wave. Robinson and Wilson [8] injected tincture of digitalis into cats. They injected one tenth of a previously determined minimal lethal dose intravenously every ten minutes, and made electrocardiographic tracings at intervals of one, five and nine minutes after each injection. The vagi were intact in one series of experiments and cut in another. Their results showed that a negative T wave occurred when about one fourth of the minimal lethal dose was injected and that prolonged conduction time and complete dissociation occurred only after the administration of larger doses. These authors stated the belief that a change in the T wave is the first evidence of digitalis intoxication and that the vagi have no marked effect on the production of this change.

Other observers reported that the T wave becomes larger after injection of digitalis. Yacoel and Papanayotou [9] gave digitalis to patients with heart disease, and concluded that an increased amplitude of the T wave along with other changes are signs of improvement. Selenin,[10] using dogs under morphine narcosis, found that therapeutic doses of digitalis given intravenously caused an enlarged T wave. Bickel and Tsividis [11] used rabbits and gave Focke's extract of digitalis intravenously. They found that doses up to 1 cc. per kilogram of body weight caused an increase in the T wave, while larger quantities caused a smaller wave. In another series of experiments, Bickel and Pavlov [12] found that ordinary doses of digitalis and strophanthus caused an increase in the size of the T wave and that this wave later became negative. Similar results were obtained by Straub.[13] Nicolai and Simons [14] gave powdered digitalis in doses of 0.1 Gm. three times a day for five days. The amplitude of the wave was found increased in these persons.

METHOD

These conflicting reports suggested a series of experiments to determine the effect of varying doses of digitalis. Dogs were used at first, later cats. The

6. Harris, J.: Lancet, March 30, 1918.
7. Cohn, A. E., and Stewart, H. J.: J. Clin. Investigation **6**:53 (Aug. 20) 1928.
8. Robinson, G. C., and Wilson, F. N.: J. Pharmacol. & Exper. Therap. **10**:491 (Jan.) 1918.
9. Yacoel, J., and Papanayotou, D.: Arch. d. mal. du coeur **20**:24, 1927.
10. Selenin, W. P.: Arch. f. d. ges. Physiol. **143**:137, 1912.
11. Bickel, A., and Tsividis, A.: Biochem. Ztschr. **45**:462, 1912.
12. Bickel, A., and Pavlov, M.: Biochem. Ztschr. **48**:459, 1913.
13. Straub, H.: Ztschr. f. Biol. **53**:523, 1910.
14. Nicolai, G. F., and Simons, A.: Med. Klin. **5**:160 (Jan. 31) 1909.

animals were weighed daily and were carefully watched for vomiting and other signs of intoxication. Subcutaneous injections of ethyl carbonate (urethane) were given in sufficient doses to keep the animal quiet but not enough to cause sleep. A control dog, which had a negative T wave normally and without the use of digitalis, was given the usual quantity of urethane, and an electrocardiogram was made one hour later to determine the effect on the T wave. No change was observed. All electrocardiograms were made with needle leads, one lead being from arm to arm, the other from the base of the neck to the left groin. Chest leads were used in cats instead of the arm to arm leads, the needles being inserted at each side of the thorax, while the longitudinal leads remained the same as for dogs.

The powdered digitalis leaves were standardized. The other forms of digitalis consisted of digalen, Hoffmann La Roche; digitalin, Nativelle; digipuratum, Knoll (now described in "New and Nonofficial Remedies" as digitan), and digitalis dispert, Krause. The smaller doses corresponded to therapeutic quantities in man when calculated according to the respective weights of man and of the animals used; however, much larger, even fatal, doses were also used. The drug was also given daily to observe the cumulative effect.

Control electrocardiograms were taken before each experiment. Further tracings were taken at intervals of three, six and twenty-four hours after the administration of digitalis. The tracings in acute experiments were taken at intervals of ten or fifteen minutes for periods of about three hours and again fifteen and twenty-one hours later if the animal survived.

EXPERIMENTS

The first series of experiments consisted in noting the changes following the administration of powdered digitalis leaves by mouth with the aid of a stomach tube.

A dog weighing 4,500 Gm. was given 0.004 of standardized digitalis leaves by mouth once daily for four days. There was practically no change in the electrocardiogram except a slowing of the heart rate from 275 to 195 per minute. The T wave remained the same as in the control.

Another dog, weighing 7,000 Gm., received 0.008 of powdered digitalis leaves in the same way for four days. Larger doses were then tried. A dog weighing 5,100 Gm. was given 0.016 of digitalis for four days. A male dog, weighing 5,900 Gm., received 0.024 daily for three days, then 0.048 twice daily for two days and then 0.104 once on the next day, making a total of 0.368 in six days. Another dog, weighing 4,400 Gm. was given 0.032 once daily for three days, then 0.128 daily for two days, making a total of 0.352 in five days. In the electrocardiograms made of the foregoing animals, the T wave occasionally increased in amplitude by 1 or 2 mm., but this was rare. In none of these tracings was there a reduction in the amplitude of the T wave, and the wave never became negative. The only change constantly present was a definite reduction in rate, which might have been due to the fact that the animals became accustomed to the procedures.

The failure to record changes in the T wave, even after large doses of digitalis by mouth might be due, perhaps, to the nonabsorption from the gastro-intestinal tract. To exclude such a possibility subcutaneous administration was tried. A dog weighing 5,700 Gm. was given 3 cc. of digalen, Hoffmann La Roche, subcutaneously, and electrocardiograms were taken three, six and twenty-four hours later. A change was not observed, and vomiting did not occur. The animal was given 5 cc. on the next day and 5 cc. again on the day following, making a total of 13 cc. in three days. There was a slight reduction in the amplitude of the R and S, and the T wave became somewhat lower for a while, but its height at the end of the experiment was exactly the same as in the control. A negative T wave was never observed. The same animal was then given 10 cc. subcutaneously and died three hours later.

Intramuscular injections of digitalin, Nativelle, were then employed. A female dog, weighing 8,700 Gm., was given 0.5 mg. of digitalin in olive oil intramuscularly. Another 0.5 mg. was given on the next day and 1 mg. on the following day, making a total of 2 mg. in three days. The electrocardiograms, taken at intervals of three, six and twenty-four hours after each injection, did not show a deviation from those of the control tracings, and the T wave became neither lower nor negative.

The intravenous route was next chosen. A dog weighing 4,400 Gm. was given digitalis dispert, Krause; the standardized strength being 150 frog doses in 0.1 Gm. The total dose of 200 mg. was divided into small doses and given during a period of three hours. Electrocardiograms were taken every fifteen minutes. The heart rate dropped from 225 to 156 per minute, and the PR interval increased from 0.08 to 0.12 seconds. This change occurred at the end of the first hour, after 75 mg. had been injected intravenously. No additional changes occurred during the rest of the experiment or in a tracing taken fifteen hours later. The T wave did not show a change at any time, even when the heart rate dropped and the PR interval was prolonged.

Digipuratum, Knoll, was then injected intravenously. This preparation was found satisfactory and was used in all further experiments. The dog which failed to react to intramuscular injections of digitalin was used on the following day, after another control electrocardiogram had been made. The animal received 2 cc. intravenously. Tracings were made at intervals of ten and fifteen minutes for a period of two hours. Subsequent tracings were made three, twenty-one and twenty-seven hours later. There was practically no change in the electrocardiogram at any time. The same dog was used for a more acute experiment after the last tracing was taken. Electrocardiograms were taken every ten and fifteen minutes during the experiment, which lasted two hours. The first dose of digipuratum given intravenously was 4 cc. Distinct

changes were seen in the electrocardiogram in thirty minutes. The heart rate dropped from 168 to 96; the PR distance was increased from 0.08 to 0.12 seconds, and the amplitude of the T wave was reduced from 4 to 2 mm. The value of this reduction is doubtful, as a control tracing from the same dog, taken four days earlier, showed a T wave of only 3 mm. A change of 1 or 2 mm. seems indecisive. Another injection of 2 cc. did not produce further changes in the wave, but the amplitude of R and S was reduced. Another dose of 4 cc. was given, and ventricular tachycardia occurred. The animal died shortly afterward. This experiment showed that a negative T wave did not appear, and that this wave became reduced only by 1 or 2 mm. even though the drug was given until death was caused. The slight variability in the electrocardiogram taken for control on different days discounts an equally slight change in the T wave after the administration of digitalis.

Another dog was given smaller doses of digipuratum intravenously, and electrocardiograms were taken every fifteen minutes for two and a half hours and again in sixteen hours. The animal weighed 6,200 Gm. and received 2 cc. as the first dose after a control tracing had been made. Vomiting occurred in five minutes, but there was no change in the electrocardiogram at this time. Another injection of 2 cc. was given thirty minutes later, and an electrocardiogram taken thirteen minutes after this dose showed definite changes. The heart rate dropped from 195 to 120, the PR interval increased from 0.06 to 0.16 seconds and there was marked sinus arrhythmia at times; heart block and escaped beats were present and ventricular extrasystoles were seen. All of these changes appeared at the same time; none was present before. The T wave was unchanged. A further dose of 1 cc. was given thirty minutes after the last one, and the T wave remained unchanged. The other signs of toxicity persisted. Another dose of 1 cc. was then given, making a total of 6 cc. for a dog weighing 6,200 Gm. in a period of two and a half hours. Ventricular tachycardia now developed. A tracing taken fifteen hours later showed a return to sinus rhythm, but the PR interval was still 0.04 seconds longer than on the control tracing. The T wave was unchanged, slightly higher if anything. The digipuratum in this experiment was given until definite toxicity occurred, but the T wave never became negative. In fact it was slightly higher at the end than at the beginning of the experiment. An interesting feature was the fact that none of the dogs that received digitalis developed coupled beats. Even toxic or fatal doses failed to produce this phenomenon in contrast to the frequent occurrence in cats.

A similar but smaller series of experiments was made on cats. Digipuratum was given intravenously at intervals of thirty minutes, and electrocardiograms were taken every ten or fifteen minutes for the

two and a half or three hours that the experiments lasted. The cats were weighed and received sufficient doses of ethyl carbonate (urethane) subcutaneously to keep them quiet but not enough to put them to sleep. Needle leads were used as previously described. Control tracings were taken before the drug was given.

A cat, which weighed 2,100 Gm., was given 2 cc. of digipuratum intravenously and tracings were made at fifteen minute intervals for a period of three hours. Salivation and vomiting occurred in seven minutes, and the electrocardiogram taken fifteen minutes after the injection showed idioventricular rhythm. Another tracing taken fifteen minutes later still showed idioventricular rhythm, but the ventricular beats were of two varieties, one form alternating with the other, forming coupling. Later records showed complete block, but the T wave remained positive except in two tracings in which the T wave was diphasic. A distinctly negative T wave was not seen although there were signs of severe intoxication before the wave reappeared in conducted beats. The animal subsequently developed ventricular tachycardia.

Another cat weighing 3,800 Gm. was given digipuratum intravenously in smaller doses, which were repeated. The experiment was performed as with the first animal. The first dose was 0.5 cc. and the heart rate was reduced from 210 to 165 per minute. The T wave was positive in the chest leads of the control and negative in the longitudinal lead of this curve. The wave became iso-electric in the first lead thirty minutes after the injection and remained slightly negative for the remainder of the experiment. The longitudinal lead remained practically unchanged. Other signs of intoxication developed, such as vomiting and finally idioventricular rhythm, which in places consisted of coupled ventricular beats of different types. This animal received a total of 1.5 cc. of digipuratum intravenously.

A cat weighing 2,200 Gm. received 0.5 cc. of digipuratum intravenously and then 0.25 cc. every thirty minutes until a total dose of 1.25 cc. was given. The heart rate fell from 216 to 168. The R was reduced from 6 mm. to nearly zero, and the T wave became negative fifteen minutes after the first dose. Complete block and idioventricular rhythm appeared later, in seventy-five minutes. This animal also showed coupling of two different varieties of ventricular beats.

A cat, which weighed 2,900 Gm., was given digipuratum intravenously under the same conditions as the previous animals until a total of 1.75 cc. was administered. The heart rate was decreased only slightly; the R gradually became smaller, from 14 mm. in the control to 5 mm. The T wave at first became slightly negative and then returned as a positive wave about thirty minutes before idioventricular rhythm set in.

COMMENT

Experiments on dogs in which various preparations and doses of digitalis were given by different routes showed results which were different from those reported by other investigators. The report of Cohn and Stewart,[7] which stated that dogs which received sufficient amounts of digitalis constantly showed changes in the T wave, could not be corroborated. There is no question of sufficiency of dosage in my experiments, as the dogs showed other evidences of intoxication, such as heart block, auriculoventricular and ventricular rhythms and vomiting. In some instances, the drug was given until death resulted.

These experiments on dogs also showed that several of the electrocardiographic evidences of intoxication all appeared at about the same time. This is in contrast to the results of Robinson and Wilson,[8] who experimented on cats and found that a change in the T wave preceded block and dissociated rhythm. The fact that different animals were used must be kept in mind.

Another interesting feature was that coupling was not observed in dogs regardless of the quantity of digitalis given. This is in contrast to the results obtained with cats.

The rapidity of intravenous action was demonstrated in dogs when sufficient quantities were given. A dog that received 4 cc. of digipuratum intravenously vomited in thirteen minutes, and heart block was present thirty minutes after the injection.

A constantly negative T wave was not observed in a single instance in dogs in spite of the fact that sufficient quantities were given to produce distinct signs of marked toxicity. It may be stated in passing that some animals are more susceptible to digitalis than others of the same species. Magnus[15] told of two varieties of cats from the same city, one being more resistant to digitalis than the other. This can hardly be the case in my experiments, as there were many other evidences of toxicity showing that the drug was sufficiently effective.

These results throw some doubt on the advisability of using the T wave as a criterion of the activity of digitalis in man. It is, of course, an open question whether the results of experiments on dogs can be transferred to man, but the failure to observe a negative T wave in a single instance and the reports previously mentioned on man, which contradict the statement that a change in the T wave is a sign of digitalis action, seem to show the advisability of at least further study on this question before definite conclusions can be reached.

The experiments on cats were less clearcut and of less value because a smaller number of animals were used. Unforseen circumstances made it imperative to cut short the experiments. It may be stated,

15. Magnus: Arch. f. exper. Path. & Pharmakol. **135**:283 (Oct.) 1928.

however, that a negative T wave was not a constant observation even though the amount of digitalis was pushed to extreme toxicity. A serious objection also is the fact that the T wave was negative at one time and later positive during the same experiment after more of the drug was given. Further study is necessary before definite conclusions can be drawn in this respect.

SUMMARY

1. Dogs were given various preparations of digitalis in different doses and by various routes. The quantities given varied from what would correspond to therapeutic doses to quantities causing definite toxicity and death.

2. Electrocardiograms taken at frequent intervals and over a long period of time failed to show a constantly lowered T wave. The wave was never seen to be negative.

3. Intravenous administration produced effects in a few minutes when the dose was sufficiently large.

4. It seems an open question whether the T wave can be used as a criterion of the action of digitalis.

5. Experiments on a small series of cats produced variable results. The T wave sometimes became negative and at other times remained unchanged. The observation that the wave may become negative for a time and then return as a positive wave after more digitalis was given seems to point to the necessity for more study with these animals.

OPIUM ADDICTION

IV. THE BLOOD OF THE HUMAN ADDICT DURING THE ADMINISTRATION OF MORPHINE *

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In this paper, we present the data obtained from the study of blood drawn from a series of human addicts receiving morphine sulphate hypodermically in sufficient quantity to prevent withdrawal symptoms. All of these addicts exhibited the so-called withdrawal symptoms on cessation of administration of the drug. These symptoms have been described in a previous paper by us [1] and are well known to any one familiar with the drug problem. Our purpose in this study has been twofold. The first objective was to search for possible changes in the physicochemical properties of the blood of these addicts; our second, to obtain values in addicts receiving the drug for comparison with the results obtained from the same addicts following the withdrawal of the drug.

EXPERIMENTAL PROCEDURE

During this study the addict received the quantity of drug required, which was administered to him by the nurse in charge of the ward. As a rule, the same quantity sufficed from day to day for each subject, but any minor disturbance in the ward on the part of other refractory patients always resulted in a need for a greater amount. This variation of dosage is common among addicts at liberty with a supply of the drug at hand. The slightest degree of fear on their part always resulted in a temporary increase in dosage. The dosage of the drug in the cases studied varied from 6 to 30 grains (0.4 to 1.95 Gm.) of

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* From the Narcotic Wards of the Philadelphia General Hospital.

* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City. The research was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction in the wards of the Philadelphia General Hospital, which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

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morphine sulphate a day. The average dosage was about 20 grains (1.3 Gm.) a day.

All samples of blood were collected in the morning before breakfast while the subjects were at rest in bed. The blood was always drawn from one half to one hour after the last dose of morphine had been given. The method of collection followed was that of the investigators whose method was employed for the determination of the particular substance to be studied. Venous samples were drawn from a vein at the elbow, usually without the aid of a tourniquet; occasionally, the size of the vessels and failure to obtain enough blood without the use of the tourniquet made us resort to its aid. All estimations were begun and carried to completion immediately after the samples were obtained. The patients selected were men and were free from any abscesses or intercurrent infections.

METHODS

To determine the hemoglobin the blood was converted to acid hematin and read colorimetrically with the Newcomer plate. The first ten readings were checked with the polariscope.[2]

The red and white blood cell counts were made by the same person. In each case, two pipets were counted. The count was repeated if variations of 10 per cent or over were observed in counts within the normal range, or in variations of 5 per cent outside the normal range.

Differential counts were all made by the same person. From 200 to 400 cells were counted in each determination.

The volume of the red blood cells was determined by the hematocrit method, oxalated blood being used. In our experience, this method gives lower values than the centrifuge method.

In the Wassermann reaction of the blood, cholesterol and Noguchi antigens were used.

The specific gravity was measured with a 1 cc. pyknometer at 20 C.

The plasma protein was determined by a modification of the method of Howe.[3] The dry matter was determined by desiccation of 1 cc. at 105 C. to constant weight. The dry matter of the cells was calculated and is subject to appreciable error. The hydrogen ion concentration was determined by the method of Hawkins.[4] The carbon dioxide capacity of the plasma was calculated according to the method of Van Slyke and Cullen.[5]

The serum conductivity was measured with the Christiansen ionometer, expressed in milligrams of sodium chloride and corrected by the formula of Gram and Cullen.

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Determinations were made of the sugar,[6] urea nitrogen,[7] creatinine,[8] uric acid,[9] cholesterol,[10] sodium chloride,[11] lactic acid[12] and serum calcium.[13]

The serum magnesium was determined by precipitation of the magnesium as the ammonium magnesium phosphate and the determination of phosphate as given in the next paragraph.

The serum phosphate was expressed as milligrams of phosphorus per hundred cubic centimeters and was determined by the Benedict and Theis modification of the Briggs method.[14] The oxygen content was determined according to the procedure of Van Slyke and Stadie.[15] The sedimentation test used was that of Cooper.[16]

RESULTS

Tables 1, 2 and 3 contain our observations in a form designed to condense them as much as possible. The tables give the normal variations for the substances investigated, the number of cases studied, the maximum, minimum and average figures, and the number deviating beyond the normal range. The number of patients studied varied greatly. Studies of the blood were continued only until we felt that we had a sufficient number of cases to establish the average and variations in addicts while they were receiving morphine.

A series of sedimentation tests done on twelve addicts are not shown in the tables. The results coincided closely with the average normal curves of Cooper.[16] Five different patients were selected for a study of the fragility of the red cells. Beginning hemolysis, from 0.44 to

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TABLE 1.—*The Cellular Elements of the Blood of Addicts During the Administration of Morphine*

	Hemoglobin, Gm. per 100 Cc.	Red Blood Cells, Number per C.Mm.	White Blood Cells, Number per C.Mm.	Differential Count, per Cent					Red Blood Cells, per Cent by Volume	Blood Wassermann Reaction
				Polymorphonuclears	Lymphocytes	Large Mononuclears	Eosinophils	Basophils		
Normal variation	14.5–17	4,500,000–5,200,000*	6,000–9,000*	58–70*	25–35*	1–6*	0–2*	0–2*	38–45	
										Positive 3
Maximum	19.4	4,960,000	15,400	78	63	7	3	2	38.7	Negative 28
Minimum	12.0	3,640,000	2,500	33	20	0	0	0	34.0	
Average	15.2	4,583,000	9,300	61	34	3	½	½	36.2	
No. of cases	(26)	(29)	(33)	(28)	(28)	(28)	(28)	(28)	(6)	
No. of cases below normal range	9	23	1	5	6	6	0	0	5	
No. of cases above normal range	3	0	15	0	2	2	0	0	0	

* Normal figures arrived at by one of us in making counts on normal persons.

TABLE 2.—*The Physical Properties, p_H and Carbon Dioxide Capacity of the Blood of Addicts During the Administration of Morphine*

	Specific Gravity		Plasma Protein, per Cent	Dry Matter			Conductivity of Serum	p_H of Plasma	Carbon Dioxide Capacity of Plasma, per Cent by Volume
	Blood	Plasma		Blood, per Cent	Plasma, per Cent	Cells, per Cent			
Normal variation	1.045–1.075	1.0237–1.0276	6.5–8.2	19–23	8–10	33–36	130–139	7.30–7.50	55–75
Maximum	1.0614	1.0282	8.3	22.7	10.2	48.0	143	7.51	71
Minimum	1.0557	1.0238	6.9	15.7	5.3	38.2	132	7.28	45
Average	1.0586	1.0260	7.8	20.1	8.4	41.2	137	7.36	57.7
Number of cases	(5)	(7)	(8)	(22)	(15)	(7)	(7)	(20)	(20)
Number of cases below normal range	0	0	0	1	4	0	0	1	5
Number of cases above normal range	0	1	2	0	1	7	1	1	0

TABLE 3.—*The Chemical Properties of the Blood of Addicts During the Administration of Morphine*

	Blood Sugar, Mg. per 100 Cc.	Blood Urea Nitrogen, Mg. per 100 Cc.	Blood Creatinine, Mg. per 100 Cc.	Blood Uric Acid, Mg. per 100 Cc.	Blood Cholesterol, Mg. per 100 Cc.	Blood Sodium Chloride, Mg. per 100 Cc.	Blood Lactic Acid, Mg. per 100 Cc.	Serum Calcium, Mg. per 100 Cc.	Serum Magnesium, Mg. per 100 Cc.	Serum Phosphate, Mg. Phosphorus per 100 Cc.
Normal variation	70–120	10–15	1–2	2.3–5	150–190	450–530	5–20	9–11	2–3	3–4
Maximum	122	24.0	1.3	4.5	280	570	31.13	14.4	2.12	3.2
Minimum	72	10.0	1.085	2.4	158	444	20.10	9.8	2.06	2.6
Average	97	13.2	1.160	3.3	208	495	25.75	10.9	2.09	2.8
Number of cases	(32)	(28)	(3)	(22)	(21)	(13)	(6)	(14)	(2)	(11)
Number below normal range	0	0	0	0	0	1	0	0	0	7
Number above normal range	1	3	0	0	15	2	6	4	0	0

0.48, and a complete hemolysis, from 0.32 to 0.36, were observed in all cases. These figures fall within normal limits. Clotting time was determined by noting the beginning of coagulation in a capillary tube. The time was noted when a soft clot was seen after the tube was broken. The average coagulation time in six cases was found to be two minutes and thirty seconds. The viscosity of whole blood was measured in five different cases by means of the Hess viscosimeter. The average viscosity of the blood was 5.18 compared to that of distilled water at a temperature of 25.4 C., the normal range being from 4.3 to 5.2. In three cases blood was drawn from the right radial artery, and the percentage saturation of the hemoglobin with oxygen was determined. The average percentage saturation in these three cases was 94.6, well within normal figures.

COMMENT AND LITERATURE

The results obtained show data for a large number of the determinations that are well within the normal range. Certain constituents show a rather marked deviation and will be mentioned in the following discussion. We have not found any correlation between length of addiction, daily dosage, age and these deviations.

Cellular Elements.—We were unable to find any evidence that opium addiction per se brings about any decided decrease in the number of red cells of the blood. Our observations are in accord with those of Morat [17] and of Lambert and Tilney.[18] Morat counted the red cells in twenty-nine cases and found an average count of 5,037,000, an average white cell count of 9,300 compared to our average of 4,533,000 red cells and 9,300 white cells per cubic millimeter of blood. Lambert and Tilney [18] reported a variation of red cell counts between 4,300,000 and 4,890,000 per cubic millimeter in addicted subjects before instituting the narcosan treatment. Fuller [19] reported a single red cell count made on the blood of a heroin addict and found the number of red cells to be about 2,000,000. Gunard and Devay [20] reported a red cell count of 2,300,000 per cubic millimeter in a dog addicted to morphine for a period of six and one half months. Plant and Pierce [21]

17. Morat, D.: Le sang et les sécrétions au cours de la morphino-manie et la desintoxication, Paris, G. Steinheil, 1911, pp. 180.

18. Lambert, Alexander; and Tilney, Frederick: Treatment of Narcotic Addiction by Narcosan, M. J. & Rec. **124:** 764 (Dec. 15) 1926.

19. Fuller, S. C.: A Phenomenon Observed in the Blood of Morphinomaniacs, New England M. Gaz. **34:**241, 1899.

20. Gunard and Devay, F.: Observation d'un cas de morphinism chronique chez un chien, J. de med. vet. et de zootech. **19:**261, 1894.

21. Plant, O. H., and Pierce, I. H.: Studies of Chronic Morphine Poisoning in Dogs: II Changes in Blood Cells and Hemoglobin During Addiction and Withdrawal: III. Blood Sugar During Tolerance and Withdrawal, J. Pharm. & Exper. Therap. **33:**359 (July) 1928.

studied the blood cells of dogs which without question were really addicted for periods ranging from one to two years. They did not find variations from those of normal dogs. Our low figures were obtained from persons who lived in poor hygienic surroundings and who unquestionably suffered from lack of nourishing food due to the fact that practically all of their funds were used for drugs. The great variation in the white cell counts is difficult to explain. Morat [17] also found the same rather large variation of white cells—from 8,000 to 14,000. Our patients were free from abscesses and had normal temperatures and pulse rates. We have seen a variation of from 8,000 to 14,000 white cells per cubic millimeter in a period of three days in a patient receiving a sufficient amount of the drug.

Chemical Elements.—Our results are in accord with those of Lambert and Tilney [18] and of Johnson [22] for human addicts and those of Plant and Pierce [21] for addicted dogs. The variations of hemoglobin reported by Lambert and Tilney [18] expressed in percentage varied between 70 and 80 were made, we understand, in addicts receiving the drug. Fuller,[19] however, in a single determination of the hemoglobin by means of the Fleischl method, reported the presence of only 20 per cent in the heroin addict he studied. Johnson [22] found only one abnormal blood sugar value in a series of twenty-four cases. Plant and Pierce [21] did not find any change in the blood sugar in their addicted dogs. The total blood cholesterol content shows a tendency to be above normal in the majority of our cases. Lactic acid is above the average normal. A number of the results of determinations of plasma inorganic phosphate are below the accepted normal of 3 mg. per hundred cubic centimenters of serum.

Physical Properties.—Our observations here, too, fall within the range of normal variations. Sollier [23] reported an increase in the viscosity of the blood when the number of red cells was increased in human addiction. We do not find any increase in the viscosity of the blood nor do we find any increase in the red cells. Stern-Piper [24] found the rate of sedimentation increased in nine and decreased in one of ten addicts receiving the drug. Our figures do not reveal any abnormality in this phenomenon. Morat [17] reported a diminished resistance of the red cells but gave as his normal value for complete hemolysis 0.30 and for beginning hemolysis 0.38. Our figures coincide with the figures taken as normal for these solutions in healthy subjects in this hospital.

22. Johnson, George S.: The Use of Narcosan in the Treatment of Drug Addiction, Colorado Med. **24**:347 (Nov.) 1927.

23. Sollier, P.: Recherches sur la viscosité sanguine dans l'intoxication morphinique, Bull. Acad. de méd., Paris **87**:428 (April 18) 1922.

24. Stern-Piper, L.: Die Senkungsgeschwindigkeit des Blutes bei chronischem Morphinismus und Eukodalismus, Klin. Wchnschr. **4**:548 (March 19) 1925.

CONCLUSIONS

A series of addicts receiving morphine sulphate hypodermically have been studied with respect to the following determinations: hemoglobin, red blood cell count, white blood cell count, differential count, sedimentation rate, blood viscosity, cell volume, Wassermann reaction, specific gravity of the blood and plasma, plasma refractive index, dry matter of the blood and plasma, plasma p_H, carbon dioxide capacity of the plasma, serum conductivity, sugar, urea, creatinine, uric acid, cholesterol, chloride and lactic acid of the blood and calcium, magnesium and phosphate of the serum.

In a general way there is a tendency toward a low red cell count and a high leukocyte count, but this is not uniform in all cases. The cholesterol content was usually increased and the phosphate diminished. The lactic acid content was uniformly high. No other constituents showed any suggestive departure from the normal.

A slight degree of anemia may be present when the addict is forced to live in poor hygienic surroundings when all his funds are required to purchase the drug at the expense of sufficient nourishing foods.

THE RÔLE OF ALLERGY IN TUBERCULOSIS*

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DEFINITION OF ALLERGY

When the animal body becomes infected with tubercle bacillus, its reactive powers soon become profoundly altered. This deep-seated alteration is in many respects imperfectly understood, but it manifests itself in at least two important ways. In the first place, tubercle bacilli cannot thrive as well in the previously infected body as in the normal one, i. e., an immunity is developed which, while admittedly incomplete, is nevertheless of the greatest importance in restraining the growth of, and preventing further invasions by, the bacillus. In the second place, this immune body is abnormally susceptible to protein derived from the body of the tubercle bacillus. Locally, amounts of tuberculoprotein that are rather harmless to the normal body produce necrosis of tissue and intense inflammation in the infected one. Intravenously, amounts that will be ignored by the normal body promptly produce fever, prostration and even death in the infected one. In other words, after infection the body becomes hypersensitive, or "allergic," to the protein of the bacillus. In the pathogenesis of tuberculosis, this allergic condition plays a rôle which is no less important than that of immunity. It is a direct agent of tissue destruction; its presence or absence determines to a considerable degree the character and the extent of the lesions and symptoms which will result from infection with the tubercle bacillus; and there are many who believe that it is only through allergy that immunity can operate.

It is important to define clearly at the outset just what phenomena are to be included in the term "allergy," for different writers mean somewhat different things when they speak of the "allergic reaction." All recognize that the allergic body reacts more violently to the bacillus than does the normal one, but whether the difference in reaction is qualitative or merely quantitative, whether allergy includes immunity or is a process quite separate from immunity, whether the local fixation of bacillary antigen is or is not a function of allergy—these and numerous other matters are regarded in different ways by different investigators, and are all too frequently treated vaguely and even inconsistently.

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Although the term "allergy" signifies, broadly, a condition of altered reactivity, when applied to bacterial infections (and especially to tuberculosis) custom rather limits the use of the term to certain tissue reactions and constitutional symptoms which are quite different from those associated with anaphylaxis. This is a result of the work of Baldwin, Zinsser and others who have clearly shown that an animal may be highly anaphylactic to tuberculoprotein, falling into anaphylactic shock in the characteristic way when tuberculin is injected intravenously, and yet possess no capacity to exhibit a tuberculin reaction when tuberculoprotein is injected locally; and, conversely, an allergic animal, giving a brilliant local tuberculin reaction, may not be anaphylactic at all, although the intravenous injection of tuberculoprotein will cause grave symptoms, quite different, however, from those of anaphylactic shock. In this paper, therefore, anaphylaxis will not be included in the term "allergy."

Whatever the ultimate meaning and function of allergy may be, this much can be said with certainty: The infected body becomes changed in some manner which renders the relatively bland protein of the tubercle bacillus capable of acting on its tissues as a powerful irritant and poison. As a result of this change, the cells of the allergic body are more extensively damaged and killed by a given amount of tuberculoprotein than are the cells of the normal body, and, furthermore, because of this enhanced irritant action of tuberculoprotein on allergic tissues, and because of the resulting more extensive damage and death of cells, there appears a more violent acute inflammation at the site of action of tuberculoprotein in the allergic body. More prompt and extensive damage and death of cells and more extensive acute inflammation constitute, therefore, the local visible expression of the action of allergy. Constitutionally, the greater irritative effect of tuberculoprotein on the allergic body is manifested by the fact that fever, malaise, prostration and death can ensue when an amount of tuberculoprotein which is harmless for the normal body finds its way into the blood stream of the allergic one. I think that it is important to realize clearly that everything which happens at the site of an uncomplicated allergic reaction is merely the standard reaction of the body to a chemical irritant. It is no curious or new type of reaction. With properly adjusted concentrations, it would be impossible to differentiate histologically between the site of a tuberculin reaction and a site into which one had injected sulphuric acid. I do not mean to imply here that tuberculoprotein itself acts as the irritant to the allergic tissues. Of that, one cannot yet speak with certainty. But it is certain that some substance, irritating and poisonous to the allergic body, is present at the site of an allergic reaction, and I shall speak later of the nature of this irritant.

The more intense inflammatory response of the allergic body, as contrasted with the usual leisurely appearance of a tubercle following the introduction of bacilli into the tissues of the normal body, has led numerous competent investigators to believe that the allergic body has acquired, through infection, the capacity to react to the tubercle bacillus in a manner which is different qualitatively from that in which the normal body is able to react to that organism. One authority, for example, has recently written that when bacilli are introduced into the tissues of the normal body the development of a nodular tubercle is "the *only* anatomical response which such tissues will make," and that this response is not essentially modified by the numbers of bacilli introduced.

As for acute inflammation, the same writer has stated:[1] "We never meet with inflammation in tuberculosis except in the allergic animal." In other words, the allergic body has acquired the power to react to the tubercle bacillus with acute inflammation—a power which the normal body did not possess.

I cannot share this view. The experimental studies which Dr. McCordock and I have carried out leave no doubt in our minds that either the allergic or the normal body can respond to the bacillus with either tubercle formation or acute inflammation, and that the number of bacilli and their site of lodgment are of great importance in determining the character of the reaction. One or two bacilli deposited in certain tissues of even a highly allergic body may call forth only tubercle formation; on the other hand, while even moderate numbers of bacilli can call forth acute inflammation in the normal body, larger numbers always do. It is, however, clear that the acute inflammatory response of the allergic body to any given dose of bacilli will tend to be much more intense than that of the normal one. This is a result of the fact that, in addition to any inherent irritative property of the tubercle bacillus, tuberculoprotein acts as a far more powerful irritant in the hypersensitive body. Our most careful histologic studies have failed to reveal the slightest qualitative difference between the character of the local reaction of the normal and the allergic body to the tubercle bacillus, if such factors as time, the character of the infected tissue and the numbers of organisms are taken into account.

RELATION OF ALLERGY TO ACCELERATED TUBERCLE FORMATION

I have said nothing about "accelerated tubercle formation" as a part of allergy for the reason that, fundamentally, I do not believe that it is. In 1914, Rist and Rolland[2] observed that the injection of a small num-

1. Krause: Am. Rev. Tuberc. **15**:137, 1927.
2. Rist and Rolland: Ann. de méd. **2**:13, 1914.

ber of tubercle bacilli into the skin of an allergic animal was followed, not by severe inflammation and necrosis, but by the development of a nodule, or tubercle, comparable to that formed in the skin of a normal animal as a response to a few bacilli. However, in the allergic animal this nodule developed somewhat more rapidly. Krause and Peters [3] confirmed this observation in a careful series of experiments, and the phenomenon has since become familiar to every observant student of the allergic reaction. It is this more rapid development of a tubercle in the allergic body that has come to be called "accelerated tubercle formation" and to be regarded as a form of the allergic reaction. At the risk of being regarded as attempting to erect distinctions that are not differences, I must draw into question the propriety of the universal acceptance of accelerated tubercle formation as an integral part of the allergic reaction, for although the phenomenon undoubtedly occurs as described, I believe that it is an accidental result of the allergic reaction rather than a part of it. In the Arthus phenomenon, in which nonbacterial proteins can serve as the antigen, and in every known example of bacterial allergy, the local tissue reaction is fundamentally the same, namely, damage to the cells, ordinary acute inflammation and, if the dose of antigen is large enough, death of the cells. It is true that the rapidity and the intensity with which these effects follow the application of the antigen are different in different cases. In some instances, furthermore, the acute inflammatory exudate will be predominantly serous, while in others it will be purulent, perhaps. The cells of the exudate may vary in type; the tissue cells may be merely irritated; they may be damaged, or they may be killed outright. But there seems to be a single fundamental mechanism underlying allergic tissue reactions, no matter what the antigen may be; and, no matter what the antigen, the tissue reaction is always fundamentally the same; that is, the standard reaction of the body to a chemical irritant. It therefore clouds, somewhat, the concept of allergy if one gathers into the term everything that happens when the hypersensitive body is exposed to the complex body of the tubercle bacillus. It is known that the allergic reaction is called forth by the protein part of the bacillus, and that when tuberculoprotein alone is injected into the allergic body cellular damage, necrosis and inflammation result, but never tubercle formation. It is well known that tubercle formation is a result of the presence not of soluble tuberculoprotein, but of the lipoid part of the bacillus. None of the lipoid is needed to elicit the allergic reaction; nor can one produce the allergic reaction by injecting the lipoid alone into the allergic body. If, however, the lipoid happens to be present by the side of tuberculoprotein, wandering cells attracted rapidly to the spot by the action of the protein will engulf the lipoid

3. Krause and Peters: Am. Rev. Tuberc. **4**:551, 1920.

and form tubercles. It is extremely probable, although I have never attempted to demonstrate it, that any nonspecific foreign body tubercle would be formed with greater rapidity if the inert particulate matter were injected together with an inflammatory irritant, and this merely because the wandering cells would be more rapidly attracted to the spot. But it is in no sense justifiable to confuse the process of acute inflammation with that of tubercle formation. Acute inflammation is a complicated, specific type of reaction, and tubercle formation is a separate, different process. Acute inflammation involves primarily a vascular reaction and does not imply any tendency to the formation of tubercles. On the other hand, the tubercle requires no inflammatory vascular paralysis for its evolution. It is, phylogenetically, the most primitive organized form of reaction to invading organisms, and occurs in lower animals which possess no circulatory system and in which, therefore, acute inflammation is out of the question. Tubercles can be formed independently of blood vessels in any tissue in which mononuclear phagocytes are present and, indeed, even in vitro on a cover slip in tissue cultures. Since, in tuberculosis, they are a response only to the lipoid of the bacillus and since that lipoid cannot itself elicit the allergic reaction, one must regard accelerated tubercle formation as merely an accidental complication of the presence of the lipoid at the site of action of tuberculoprotein, and not as a specific type of expression of the allergic mechanism.

The objection which I have raised is not an idle or scholastic one. It is made in the attempt to remove, as far as possible, all extraneous and confusing matters from the concept of bacterial allergy, and to emphasize the fact that local hypersensitive reactions to protein are, in essence, all alike, regardless of what protein serves as the antigen. They are all alike in that they all consist in irritation, damage, or death of cells, and in ordinary acute inflammation. At the least, I would urge a thorough and separate inquiry into the mechanism of every additional phenomenon which may be observed to happen in association with allergy before it is complacently regarded as an integral part of the allergic mechanism.[4]

RELATION OF ALLERGY TO LOCAL FIXATION OF BACILLI

From such a standpoint, let us examine the relation of allergy to the alleged local fixation of tubercle bacilli in the immune body. Since the

4. From this point of view, it is clear that the present tendency to speak glibly of the lesions of rheumatic fever as "allergic manifestations" of infection with a streptococcus may justly be regarded with suspicion. While it is always possible that the acute inflammatory lesions in this disease may be associated with allergy, the specific Aschoff body is a completely different sort of reaction and should, for that reason, even if one is willing to ignore its astonishing specificity, point to the presence of some, as yet undiscovered, specific etiologic agent at the site, capable of producing a lesion of the character of the Aschoff body.

early studies of Koch, innumerable experimental observations have suggested that the spread of viable bacilli from a local focus of reinfection is interfered with in some way in the immune body. Krause and Willis [5] have made an especially careful study of this matter. Their method, briefly, was this: A measured number of virulent bacilli were injected into the skin of normal animals and of animals which had been previously made immune by an injection of bacilli of low virulence. At frequent intervals following the introduction of the virulent bacilli into the skin, the lymph nodes draining the sites of cutaneous infection were excised, and inoculated into fresh animals, in order to find out whether or not they contained tubercle bacilli, and thus to determine whether, in the immune animals, there had been any delay in the escape of the bacilli from the cutaneous site of inoculation. These authors found that the nodes taken from the normal, nonimmune animals contained living bacilli as early as twenty-four hours after the injection into the skin; but the nodes draining the infected skin areas of the immune animals were not infective before the end of two weeks after the cutaneous inoculation. Their conclusion was, therefore, that when tubercle bacilli enter the tissues of an immune animal they are held fixed at the site where they lodge for a considerable length of time, and their spread throughout the body is correspondingly delayed, as contrasted with the rapid spread of the bacilli in the nonimmune animal. This is what is meant by the term "local fixation" of bacilli. While it is entirely possible, especially in the light of Opie's work on nonbacterial antigens, that many kinds of bacteria may be held fixed at the site of their entry into the immune body by some specific mechanism, so far the results of methods which have been designed to demonstrate bacterial fixation are susceptible of other possible interpretations. It must be remembered, for example, that tubercle bacilli cannot live as well, and are more rapidly destroyed in the immune body; it is therefore possible that they were not held fixed, bodily, in the skin in the foregoing experiments, but that the early lack of infectivity of the regional nodes of the immune animals was a result rather of the fact that there were too few viable bacilli within those nodes when they are excised. Certainly, we ourselves have never been able to discover any difference between the number of stainable bacilli at the site of inoculation into the skins of normal and immune animals during the first few days after the inoculation; and after that, the number of bacilli in the area in the normal animals surpasses that in the immune animals—quite the reverse of what one would expect to find if the bacilli were quickly drained from the site in the normal animals, and actually held there bodily for days in the immune animals. While there are objections to conclusions drawn

5. Krause and Willis: Tubercle **6**:438, 1925.

from the number of stainable bacilli in such experiments, there are also certain rather grave sources of error in the experiments designed to demonstrate the fixation of intact bacilli, and undoubtedly more work of a different nature must be done to settle the question. However, if one provisionally accepts the view that the bacilli are actually held fast, bodily, in immune tissues, how is this immobilization effected? In the immune body, allergy is usually present also, and consequently a more marked inflammatory reaction follows the introduction of bacilli; and it is to this allergic inflammatory reaction that the immobilization of the bacilli has been attributed by numerous writers. The inflammatory exudate has been assumed to hold the bacilli mechanically at the spot and so to prevent their spread; and this is one of the reasons why allergy has been regarded as a mechanism of immunity. I cannot discuss here the various facts which speak against the view that acute inflammation per se can prevent, so immediately and completely, the spread of bacteria. Such a discussion would lead us into the problem of why certain bacteria have an innate tendency to grow in localized colonies in the tissues of the normal body, while other bacteria tend to spread rapidly and diffusely through the tissues in spite of the most intense inflammation. It would also be necessary to consider the fact that inert particles, red cells, fragments of cells and phagocytes laden with débris are drained freely and in abundance from an area of acute inflammation, as the most cursory examination of the sinuses of regional lymph nodes will show; and, further, that the lymph drainage from a site of acute inflammation is more abundant than from the same area in its normal state. These and numerous other facts, difficult to reconcile with the alleged power of an acute inflammatory exudate to stop at once the spread of bacteria through the lymphatics, have been discussed at length in another place.[6] I can only say now that if the bacilli are actually held fixed in the immune body at the site of reinfection, it is much more probable that they are so held not by inflammatory exudate, but by some specific, precipitin-like mechanism such as that suggested by Opie to explain the local fixation of foreign protein, such as egg white, when introduced into the tissues of the sensitized body. Discussing the rôle of specific precipitation in the local fixation of protein antigens, Opie writes that, in the sensitized body, "the foreign substance, fixed at the site of injection, produces here an intense reaction."[7] I interpret that to mean that he regards the intense inflammatory reaction rather as a result of the local fixation and maintenance of local concentration of the antigen—quite the reverse from the view of Krause and others who maintain that it is the inflammatory reaction which

6. Rich and McCordock: Bull. Johns Hopkins Hosp., 1929, to be published.
7. Opie: Tubercle **7**:23, 1925.

holds the antigen fixed at the spot. I would, further, call attention to the fact that, without exception, all those who assume that it is acute inflammation which holds the bacilli fixed mechanically nevertheless admit the undeniable fact that when acute inflammation occurs about a quiescent tuberculous focus, there is a pronounced tendency, not to the immobilization of the bacilli at that site, but to their spread from it; and, as far as I can find, no attempt is made to reconcile this fact with the assumption that a severe acute inflammation can prevent the immediate spread of bacilli.

I shall not dwell further on this question except to say that there is at present no reason that I know for regarding the local fixation of bacilli as a part of the allergic reaction and, until more is learned about the matter, I believe that it is wiser to regard the two phenomena as separate and dissociable, and to try to analyze separately the underlying mechanism responsible for the immobilization of the antigen when such immobilization occurs, and that responsible for the allergic hypersensitivity of the tissues to the antigen in question.

THE MECHANISM OF ALLERGY

It is obviously of prime importance to try to understand the underlying mechanism of allergic hypersensitivity—the mechanism responsible for the fact that the tissues of the infected body are readily injured and killed by the introduction of amounts of tuberculoprotein which are relatively harmless to the tissues of the normal body. Since the actual substance introduced is the same in each case, it is clear that the allergic body has become changed in such a way that either tuberculoprotein itself now can act directly on it as a powerful irritant and poison, or else that the body has acquired the power to act on tuberculoprotein with the resulting formation of a noxious substance, which then damages the cells. Both the cellular damage and the inflammation of the allergic reaction are, as I have said, merely the manifestations of the action of an irritant to which the allergic body is susceptible. What is the explanation of this fact that tuberculoprotein is a violently irritating poison to the tissues of the allergic body?

In the light of what is known of protein hypersensitive reactions, it is generally believed that the most probable explanation of the allergic cellular damage and inflammation in tuberculosis is that they are the results of an antibody-antigen reaction, in which tuberculoprotein constitutes the antigen which reacts with an antibody formed during infection. According to this view, the cells of the sensitized body might be unchanged and normal, while the plasma and tissue fluids contained the antibody capable of acting on tuberculoprotein to yield an irritating substance, toxic for the normal cells. If this were so, the addition of tuberculoprotein to the plasma of an allergic animal should result in

the formation of a toxic substance that would cause cellular damage and inflammation in any animal, whether allergic or not. In spite of the fact that passive transfer of allergic hypersensitivity to tuberculin has been doubtful, or at least difficult and irregular, there were reports in the literature indicating that this might be the basic mechanism of allergy; therefore, several years ago we tested the possibility at some length by incubating tuberculin in various ways with plasma from allergic animals, and then injecting the mixtures into normal animals, in order to determine whether or not injurious substances had been formed as a result of the contact of tuberculoprotein with allergic plasma. We were never able to produce anything comparable to tuberculin reactions by the injection of such mixtures into the normal animal. Zinsser, likewise, recently reported similar negative results.

A second possibility to be considered is that the active antibody does not circulate freely in the body fluids, but that it is bound to the tissue cells in such a way that the antigen-antibody reaction leading to the formation of the injurious substance takes place actually within or on the cells. Zinsser feels that he has obtained some evidence that this is the case by means of injecting mixtures of tuberculin and extracts of ground up tuberculosis tissue into the skin of normal animals, but he speaks of his positive results as "irregular and occasional." [8]

Finally, it is conceivable that the production of cellular damage through allergic hypersensitivity is a result of an antibody-antigen reaction dependent on alterations in both the tissue cells and the body fluids.

For numerous reasons, into a discussion of which I cannot enter here, it was felt that experiments of the nature of those I have mentioned left much to be desired in the matter of proving or disproving the site of antibody localization; and, since it had never been proved whether or not the individual cells of the allergic body are themselves inherently changed in any manner which renders them more susceptible than normal cells to the protein of the tubercle bacillus, Mrs. Lewis and I [9] recently applied ourselves to the attempt to answer the following direct question: Is it true that, following infection with the tubercle bacillus, the individual cells of the various tissues of the body do become changed in such a way that they are more readily injured by tuberculoprotein, regardless of the character of the body fluids by which they are surrounded?

In order to answer this question, it is necessary to be able to compare by direct observation the effect of tuberculoprotein on the isolated, living cells of normal and of allergic animals; and the method naturally chosen was that of tissue culture. Only in this manner can cells be

8. Zinsser: J. Exper. Med. **44**:753, 1926.

9. Rich and Lewis: Proc. Soc. Exper. Biol. & Med. **25**:596, 1928.

kept alive for days, separated from their own body fluids, and removed from the complicating effects of circulatory, metabolic and nervous influences, and from the uncontrollable variations in antigen concentration which may result from the local fixation of the antigen. It is hardly necessary to recall how decisive was the in vitro method when it was applied to the solution of the mechanism of anaphylaxis.

It is clear that, if the bodily change underlying the allergic state is primarily a cellular one, the tissue cells when removed from the allergic body will exhibit a greater susceptibility to tuberculin even when surrounded by plasma from a normal animal. If, on the other hand, there is an antibody in allergic plasma which can react with tuberculin to produce an injurious substance analogous to anaphylatoxin, normal cells should be visibly injured when grown in such a medium, for tissue culture provides a delicate method of studying the effects of injurious substances on cells. Finally, if both a cellular change and a circulating antibody are necessary for the reaction, allergic cells should be injured when exposed to tuberculoprotein in the presence of allergic plasma, but uninjured by tuberculoprotein in the presence of normal plasma. These were the possibilities which we had before us at the outset.

Briefly, our technic was to wash thoroughly, through several changes of Locke's solution, the minute fragments of tissue which were to be used for the cultures, in order to free them as completely as possible from any adherent tissue fluids. The pieces of tissue were then placed in plasma to which tuberculin had just been added in the desired concentration. In each experiment we used cells and plasma from a normal guinea-pig, and from an allergic guinea-pig which had reacted strongly to tuberculin intracutaneously before the experiment. The cells used were white blood cells from the buffy coat of centrifugalized blood, and also the tissue of the splenic pulp, which grows readily in culture. Old tuberculin, water extract and broth filtrates of cultures of tubercle bacilli were used as antigen. As a control, the standard concentrated glycerin broth control for old tuberculin was used. This control was always entirely harmless to both normal and allergic cells in the concentrations used to control the effect of the tuberculin.

The results of these experiments, which were sharp and clear-cut throughout a series of many hundreds of cultures, demonstrated that, during infection, the individual tissue cells actually become altered internally in some manner which renders them inherently more susceptible to tuberculoprotein than they were before. Allergy, therefore, resides in the cells, and not in the body fluids. At least, no circulating antibodies are necessary for the production of the injurious local effects of allergy in tuberculosis. This is in agreement with the fact that the results of attempts to transfer tuberculin allergy passively have always been doubtful. The intimate nature of this cellular alteration remains to be solved. It cannot yet be stated with certainty that an antibody-antigen reaction takes place, but it is extremely probable that such is the case. One of the most curious circumstances relating to the problem is the

well known fact that although the allergic body is hypersensitive to tuberculoprotein extracted from the bacillus, this hypersensitiveness cannot be induced by the injection of tuberculoprotein. Whole bacilli, alive or dead, must be injected in order to set up the allergic state. Perhaps this is only because the artificial injections of tuberculoprotein have not fulfilled the conditions of its liberation and absorption during infection; or perhaps the true sensitizing antigen is not the extractable tuberculoprotein, but a parent substance present in the body of the bacillus and changed during extraction.

THE INFLUENCE OF ALLERGY ON THE CHARACTER OF LESIONS

I shall turn now to the rôle that allergy plays in determining the type of lesion which the tubercle bacillus will produce. The extent and character of any given tuberculous lesion found at autopsy have been determined by the interplay of a number of factors, chief among which are the virulence and the numbers of the infecting bacilli, the degree of native, individual and acquired resistance of the body, the degree to which allergy is developed, the character of the tissue in which the bacilli lodge, and the length of time which has elapsed since the bacilli were deposited at the site in question. Obviously, most of these factors are completely lost to one in any given case of human tuberculosis which comes under observation; but they can, for the most part, be governed or measured in the experimental animal. Dr. McCordock and I [6] have accordingly made a comprehensive study of the results of the interplay of these factors under controlled conditions. From such a study we have become able to interpret the manifold types of tuberculous lesions with a feeling of much greater security in the correctness of our interpretations than we formerly had. I cannot enter here into the general results of this investigation, but I would say that there are a number of rather simple principles governing the influence of the previously mentioned factors on the character of the lesion, and that the application of these principles allows us to forecast the effect of various experimental combinations and, therefore, to reconstruct, with better understanding, what has happened at the site of the lesions encountered in human autopsy material. As an example of the manner in which the application of these principles can further the understanding of certain types of lesions, let us consider for a moment the lesion characteristic of acute caseating miliary tuberculosis. It has long been known that when a sufficiently large number of unselected cases of miliary tuberculosis are studied microscopically, they can be divided into two groups. First, there are the cases in which true tubercles are scattered through the tissues—tubercles of the textbook variety, made up of compact aggregations of well preserved epithelioid cells and giant cells bound together by reticu-

lum. For convenience I shall call these "hard" tubercles, in contrast to the second type in which the scattered tubercles are loosely formed, and the cells composing them exhibit a marked tendency to undergo early death, so that even the most minute aggregations of cells frequently appear as small foci of caseation. The latter type I shall refer to as the "soft" tubercle. There has been not a little speculation concerning the reason for the existence of these two types of miliary tubercles. Some have thought that bacilli of different degrees of virulence might be the underlying cause of the difference in rapidity and extent of necrosis; others have regarded the soft type as an evidence of "low resistance" on the part of the body; recently, the view has been advanced that the small caseous foci are merely the very early stage of the larger hard tubercles, with central caseation. However, none of these views will stand the test of critical examination. Since the striking difference between the hard and the soft tubercle is the tendency to rapid necrosis of the cells of the soft variety, it should suggest itself at once that allergy is involved in the matter, for it is allergy which, in effect, transforms tuberculoprotein into a necrotizing poison. Can one say, therefore, that the presence of a high degree of allergy is the cause of the necrosis of the soft tubercle? Not at all. We have repeatedly found fresh, well preserved, hard tubercles in patients and animals in which allergy was at a high level at all times during the several weeks before death, as determined by repeated, graded tuberculin tests. It is at this point that one may make use of one of the simplest and most obvious of the principles relating to the effect of allergy on a lesion—namely, the principle that one or two bacilli are not sufficient to cause necrosis of any extent, even in the face of an extreme degree of allergy. That must be familiar to every one, for every one knows that a minute amount of tuberculin, such as could be obtained from one or two bacilli, would not cause a sloughing tuberculin reaction; but it was not until we deliberately applied to the question the obvious fact that both allergy and numerous bacilli are required for rapid and marked necrosis that we were able to understand the nature of the soft tubercle. Then, the injection of graded doses of bacilli into allergic and normal animals, as well as the comparison between the numbers of bacilli in hard and soft tubercules in man, soon made it clear that the soft tubercle was merely the result of the presence of large numbers of bacilli acting in the face of allergy. The difference in the number of bacilli to be found in the hard and soft types of tubercle is enormous.

This leads one to certain matters of interest from the standpoint of symptomatology. McCordock and I [6] have, in another place, offered what we believe to be very good evidence against the old view that miliary

tuberculosis is always the result of a sudden discharge of quantities of bacilli into a large vessel, and in favor of the view that many cases result from a much more gradual infection of the blood stream through microscopic vessels. In the case of the soft tubercle, however, one does find in the tissues exactly what might be expected as a result of the sudden discharge of large numbers of clumped bacilli from a caseous focus into the blood stream. Indeed, in a human case in which autopsy was performed at a very early stage of the process, such clumps were actually found in the capillaries of various tissues. It is well known that when a large number of bacilli or caseous débris impregnated with tuberculoprotein is suddenly injected into the blood stream of an allergic animal, that animal quickly develops a constitutional allergic reaction and becomes very ill. One should, therefore, expect that, in man, in the instances in which miliary tuberculosis is caused by the sudden discharge of a caseous focus into a large vessel, the accident should be heralded by a sudden, severe onset of illness, with symptoms of a constitutional tuberculin reaction; whereas, in the instances in which miliary tuberculosis arises as a result of the gradual feeding of bacilli into the blood stream, the onset should be insidious. As a matter of fact, the development of the great majority of cases of miliary tuberculosis is so gradual that the onset cannot be determined clinically, and in the great majority of cases hard tubercles containing very few bacilli are found in the tissues at autopsy. On the other hand, in reviewing the clinical histories of our cases of miliary tuberculosis in which soft tubercles were found, in each instance there was a story of a sudden, stormy onset leading to death. The sudden discharge of a caseous focus into a large vessel in an allergic individual may thus be recognized clinically by the abrupt onset of symptoms, and pathologically by the presence of soft tubercles in the tissues at autopsy.

I should like to cite another of the numerous instances in which the application of principles derived from experiments has led to a clearer understanding of the lesions produced by the tubercle bacillus. What is the pathogenesis of tuberculous meningitis? If one turns for information to the leading textbooks and to the literature, it will be found that while it is mentioned that meningitis may in rare cases result from the extension of tuberculous infection from a focus situated within the brain or within the bones that enclose the central nervous system, most cases are regarded as the prompt result of direct meningeal infection by way of the blood stream, appearing usually as a part of the widespread dissemination of bacilli during the septicemia responsible for miliary tuberculosis. This belief is, without doubt, a result of the frequent coincidence of miliary tuberculosis and tuberculous meningitis, especially in children, together with the fact that

the demonstration of an older adjacent tuberculous focus as the source of the meningeal infection has been decidedly exceptional in any routine series of cases. What, now, is the usual character of the meningeal reaction? A moment's thought of the extensive inflammatory exudate and of the widespread necrosis of the inflammatory cells and the contiguous meningeal tissues will leave no doubt in one's mind that acute tuberculous meningitis represents a model example of the allergic inflammatory-necrotizing reaction. If one applies the same simple principle which has just been invoked in the explanation of the soft tubercle, it will be realized that the violent allergic reaction observed in the meninges cannot have been produced by only a few bacilli. A great many must escape into the meningeal spaces to initiate such an allergic response. Now it is universally observed without hesitation that tubercle bacilli circulating in the blood during the course of miliary tuberculosis can readily lodge in the meninges in numbers sufficient to call forth the inflammatory necrotizing reaction. There were, however, several considerations which stimulated us to test the validity of this assumption. In the first place, we had become familiar with extreme forms of miliary tuberculosis in which, in spite of the fact that every susceptible organ was riddled with tubercles, there was no meningitis at all, not even in cases in which we knew that allergy had remained at a high level up to the time of death. Why had these allergic patients not developed meningitis if circulating tubercle bacilli readily settle out in the meninges in large numbers? In the second place, a careful study of our cases of tuberculous meningitis associated with miliary tuberculosis soon convinced us that the lesion in the meninges is by no means always of the same age as the tubercles scattered through the viscera. There were even cases in which the visceral miliary tubercles were unquestionably younger than the meningitis. Again, there were in our records the rather baffling cases in which meningitis existed in the complete absence of miliary tuberculosis and also in the absence of any discovered local tuberculous focus from which the infection could have extended. The literature has shown us that the records of our department are not unique in the experience of cases of this sort. Finally, we had never observed the development of meningitis as a direct result of the large number of experimental intravascular injections of tubercle bacilli which we had carried out for other purposes.

We therefore set about in the deliberate attempt to produce tuberculous meningitis by repeated injections of large numbers of virulent bacilli into the circulation of allergic animals. We were entirely unable to produce meningitis by this means, even when we injected clumps of bacilli directly into the carotid artery. At best there appeared here and there a few scattered tubercles in the meninges, although the

viscera in such experimental animals were studded with tubercles. It soon became clear to us that, in the guinea-pig, rabbit and dog, tubercle bacilli circulating in the blood do not tend to lodge in large numbers in the meninges. The amount of tuberculosis found in any tissue following infection by the blood stream undoubtedly is determined partly by the ability of that tissue to stop and hold any circulating foreign particulate matter, and the experiments of Brickner [10] in our laboratory have demonstrated that the meninges belong to the group of tissues which stop and hold only minute amounts of circulating particulate matter. We have found the same to be unquestionably true of circulating tubercle bacilli, and the presence of allergy does not increase the ability of the meninges to stop the bacilli. Tuberculous meningitis, then, cannot be produced as a direct result of blood stream infection in animals, and the cases of extreme miliary tuberculosis without meningitis indicate clearly that the same is true of man, for it is a fact that the relative degree of involvement of different tissues in miliary tuberculosis in man is always the same. It never happens, for example, that the spleen or the lungs are spared in a case in which the other susceptible organs are full of miliary tubercles. The fact that the meninges are not infrequently spared in such cases means only that they are never heavily infected directly from the blood.

Although we could not experimentally produce meningitis by sending tubercle bacilli to the meninges by way of the blood stream, it was, however, easy to set up typical tuberculous meningitis by the injection of bacilli directly into the subarachnoid space of allergic animals, thus fulfilling the conditions of the principle that, for the production of extensive allergic reactions, large numbers of bacilli are required.

It is evident that all these considerations made us hesitate to share the generally accepted view that, during the septicemia of miliary tuberculosis, bacilli lodge in the meninges from the blood stream in numbers sufficient to call forth the acute diffuse allergic reaction characteristic of tuberculous meningitis. Where, then, were the bacilli coming from, if not directly from the blood stream? The only other possibility was that the meninges were being directly infected by the discharge of bacilli into them from some adjacent tuberculous lesion. We therefore began to examine minutely the human material at our disposal and, by laboriously cutting the brains into very thin slices and by keeping a sharp lookout for caseous lesions, older than the meningitis, in communication with the meninges or the ventricular cavities, we found to our surprise that we were able to demonstrate such lesions in almost every case in which we had the entire central nervous system for examination. Small caseous tubercles in the cortex, although rarely numerous, are

10. Brickner: Bull. Johns Hopkins Hosp. **40**:90, 1927.

frequently present in cases in which there is a progressive visceral tuberculous lesion of any extent, even in the absence of miliary tuberculosis; for periods of mild bacillemia, with consequent dissemination of bacilli, are the invariable accompaniment of progressive lesions. Similar discrete, sparsely scattered tubercles may be found in the meninges, though more rarely than in the substance of the brain. For the production of meningitis, it is necessary only that these meningeal or cortical tubercles grow, caseate and discharge their bacilli into the meninges. Without such extension from the brain, meninges, or surrounding bones we believe that tuberculous meningitis will never occur, and we have been able to demonstrate such discharging lesions, usually multiple, in 90 per cent of the forty cases of meningitis we have studied. In the four cases in which the site of discharge was not found, we did not have the entire brain or the middle ears for examination. It must be remembered that the tubercle bacillus differs from pyogenic organisms in the important fact that it cannot multiply so rapidly. One or two pyogenic bacteria escaping into the meninges will have formed colonies within twenty-four hours, but not so with the tubercle bacillus. In the infected, immunized body one or two bacilli lodging at any site will either be killed outright or else encapsulated. Of course, not every tubercle which extends to the meninges will set up meningitis. Many of them are completely encapsulated, and this is especially true of large tubercles in the brain.

I cannot now enter into the other proofs of the correctness of this view of the pathogenesis of tuberculous meningitis which have been brought together elsewhere,[11] or do more than mention that the same principle of direct extension of infection from an adjacent lesion governs the development of tuberculous inflammatory effusions into any serous cavity. Such serous effusions are never the immediate result of blood stream infection of a serous cavity. I have offered this revision of our own attitude on the question of tuberculous meningitis only as an example of the manner in which the various principles relating to allergy, which have been established by experiment, may be applied to the clearer understanding of the pathogenesis of the most diverse forms of tuberculous lesions.

RELATION OF ALLERGY TO ACQUIRED IMMUNITY

Throughout this discussion of allergy, the effects of allergic hypersensitivity to tuberculoprotein have been repeatedly referred to in terms of tissue damage and destruction, and untoward constitutional symptoms. However, since it was learned long ago that the specific, inherited, coordinated reactions of the body usually serve the purposes of protection and survival, it is only natural to feel that the complicated

11. Rich and McCordock: To be published, Bull. Johns Hopkins Hosp.

mechanism of allergy must also exist for some serviceable end. That allergy is an agent of tissue injury—that, indeed, the only thing which is really known about the result of the action of allergy to tuberculoprotein is that it produces tissue damage—is perfectly true. But it is hardly possible to believe that acquired tissue hypersensitivity to protein is, in essence, a mechanism contrived for the survival of bacteria at the expense of the animal host. Indeed, so far from believing any such thing, the vast majority of investigators today hold the belief that the allergic state is a direct mechanism of defense against the invading micro-organism. Although it is so widely accepted as a fact, I cannot emphasize too strongly that the concept of allergy as a necessary mechanism of immunity to bacterial infection is still purely in the stage of hypothesis. To discuss the matter adequately would require more time than the bounds of this lecture permit, but I must speak about the question, however incompletely, for the problem of the exact status of allergy in relation to immunity is one of the most important matters concerned in the pathogenesis of tuberculosis. Every observant student of the disease knows well that extensive tissue destruction and constitutional symptoms are directly dependent on allergic hypersensitiveness to tuberculoprotein. It is therefore of fundamental importance not only for theoretical but also, perhaps, for practical reasons to know whether or not this hypersensitive state which, in effect, converts the bland protein of the bacillus into a most violent poison, is necessary in any way for the operation of acquired immunity.

The hypothesis that allergy is a mechanism of immunity rests, largely, on the fact that, following infection, both allergy and immunity appear about the same time and are usually coexistent thereafter. The more prompt and intense inflammatory reaction which follows the introduction of numbers of bacilli into allergic tissues has led to the belief that it is through this reaction that the bacilli are killed and prevented from spreading. In the instances in which only a few bacilli are introduced into the allergic body and no marked inflammation results, but instead a somewhat more rapid evolution of a tubercle, this more rapid encapsulation of the organisms is interpreted as a mechanism of immunity in that it, too, prevents the spread of the bacilli throughout the body. The destruction of tissue through the agency of allergy is regarded, from this point of view, as a local sacrifice, necessary for the survival of the body as a whole. In view of the unusually destructive nature of hypersensitiveness in tuberculosis, it is important to know whether or not this local sacrifice of tissue is actually necessary for the operation of immunity.

I have already pointed out that there are reasons for believing that it is not the inflammation of allergy which prevents the spread of the

bacilli. As for the great emphasis which is laid on accelerated tubercle formation as a mechanism of immunity, while it is clear that this process tends to aid mechanically in the prevention of spread of the particular bacilli enclosed in each tubercle, I believe, nevertheless, that accelerated tubercle formation is neither a necessary nor a decisive factor in acquired resistance. It is well known that mere phagocytosis and the formation of a tubercle about bacilli is not sufficient, alone, to prevent their multiplication, or else progressive infection would not even follow the intravenous injection of bacilli into the nonimmune body, for within a short time after such an injection, all of the bacilli are within phagocytic cells, and tubercle formation is well under way. Indeed, the clearest way to become convinced that the mere prevention of spread of bacilli is of little consequence in itself is to observe what happens in the immune animal after the organisms are deliberately spread throughout every tissue by the injection of a fine suspension of bacilli directly into the blood stream. Several weeks later, at autopsy, these immune animals will show few lesions, while nonimmune controls which received the same dose at the same time will have developed widespread tuberculosis, with myriads of tubercles throughout their tissues. If the suspension of bacilli is fine enough and a very small dose impacted so that single bacilli stop here and there, no appreciable allergic inflammation occurs in the tissues; and indeed, the difference in the rapidity of tubercle formation in the immune and the control animals will be truly negligible; yet the bacilli thrive in the nonimmune animals but fail to proliferate freely and die out in the immune ones, urging attention to the fact that the immune body is a poor medium for the bacillus, regardless of the allergic reaction.

What now of the idea that it is the more rapid and extensive allergic inflammation which kills the bacilli more promptly in the immune body? What I have just said indicates that, in the immune body, there must at least be some other mechanism unfavorable to the life of the bacillus, but can the allergic inflammation serve that purpose also? If it could be shown that the circulating blood of the immune body possessed potent bactericidal, lytic or growth inhibiting properties, it would be clear that it would be beneficial to have those antibodies brought quickly by inflammation to any site at which the bacilli lodge. However, up to the present, the most painstaking efforts by others as well as by ourselves have consistently failed to demonstrate that the plasma of immune animals possesses any greater power of destroying or inhibiting the growth of the bacilli than the plasma of susceptible, nonimmune animals. What, then, of the cellular portion of the inflammatory exudate? It is generally agreed, I believe, that in the normal body the polymorphonuclear leukocyte plays little rôle in the destruction of the

tubercle bacillus. The only prominent phagocytic defense which the body possesses against this bacillus is the mononuclear phagocyte, and the merest novice soon learns that the bacilli can live and multiply only too well within these cells in the normal animal. It is conceivable, however, that in the immune body these phagocytes have acquired a greater power of digesting the bacillus. Mrs. Lewis and I have, therefore, for some time been engaged in feeding tubercle bacilli in vitro to polymorphonuclear and mononuclear phagocytes taken from immune and from normal animals, but so far we have not been able to detect the slightest difference between the digestive powers of the phagocytes taken from the immune animals and those taken from the nonimmune animals. Thus, in spite of the fact that the survival and growth of the bacillus are greatly hampered in the intact, immune body, up to the present neither the fluid nor the cellular part of the blood of the immune body has been found to possess anything definitely injurious to the tubercle bacillus in vitro which does not exist in normal blood. It is therefore difficult to believe that the bringing of the blood by inflammation to the site of localization of bacilli can be the secret of immunity; and, as a matter of fact, Krause and Willis [12] have shown that the injection of bacilli into sites of prepared, acute, allergic inflammation in the immune body not only fails to bring about a more rapid destruction of the bacilli, but actually favors infection, as compared with the results of injecting the same number of bacilli into a noninflamed area. I have already mentioned the decidedly unfavorable effect of acute inflammation on latent foci of bacilli.

It is important for the present discussion that allergy and immunity do not always parallel each other in intensity. Thus, Petroff and Stewart [13] have recently shown that the allergy established by the proper injection of dead bacilli is in no respect distinguishable in intensity from that resulting from infection with living bacilli; yet the immunity acquired from the injection of dead bacilli is distinctly less than that following infection with living organisms. Furthermore, Willis [14] has shown that allergy wanes and practically disappears after the lapse of months following an immunizing infection, but the animals in which allergy is virtually absent are nevertheless found to be highly immune when inoculated with virulent bacilli. Such experiments as these are among the observations which indicate that allergy and immunity may be separable, dissociable phenomena and that the degree of immunity may not depend on the degree of allergy.

12. Krause and Willis: Am. Rev. Tuberc. **4**:563, 1920.

13. Petroff and Stewart: J. Immunol. **12**:97, 1926.

14. Willis: Am. Rev. Tuberc. **17**:240, 1928.

These experiments of Krause, of Petroff and Stewart and of Willis, although they appear to me to speak against the identity of allergy and immunity, are nevertheless the products of investigators who adhere to the view that allergy is essential for immunity. I regret that I have not sufficient time now to discuss the explanations which the respective investigators offer for these results, for they are results which are not entirely consistent with their own point of view.

The experiments which I have just cited, and also numerous other facts relating to other infections as well as to tuberculosis, must at least render one hesitant about accepting too readily the current statements about the necessity of allergy for the operation of acquired immunity, and should urge us to search further for a different and more fundamental mechanism of immunity. Even if the blood of the body with acquired resistance could be shown to possess acquired bactericidal powers, it is clear that the allergic inflammation, by bringing that blood rapidly to a spot, would only be serving as an assistant to the separate, acquired, bactericidal mechanism of immunity. It is customary, of course, to think of acquired immunity in terms of specific bactericidal antibodies, chiefly because such antibodies do play an important rôle in the acquired immunity to certain micro-organisms. It is, however, not impossible that in tuberculosis and in certain other infections the mechanism of acquired immunity consists, not in the acquisition of specific bactericidal properties, but in some more subtle incompatibility between bacterium and host which interferes with free parasitism. If such were the case, there is no reason to believe that the inflammation of allergy would in any way serve that incompatibility. That a special tendency to exudative inflammation is completely unnecessary for the successful operation of an immunity of the latter type must be obvious from the fact, observed by Lewis and Sanderson [15] as well as by ourselves, that the reaction of the normal rabbit to virulent human tubercle bacilli is as slow and leisurely and as proliferative in character as is that animal's reaction to virulent bovine bacilli; yet the latter infection progresses to a fatal termination, whereas the former is completely resisted and does not. The same is true of the reaction of the guinea-pig to the R_1 human bacillus of low virulence, as compared with this animal's reaction to a virulent strain. The lack of a difference in the histologic response of the tissues of the rabbit to the two forms of bacillus is somewhat difficult to link with the recent report of Lurie [16] that during the first few days after infection the human type of bacillus proliferates much more rapidly in the tissues of the rabbit than does the bovine type. The ultimate correlation of these observations will be of considerable interest.

15. Lewis and Sanderson: J. Exper. Med. **45**:291, 1927.

16. Lurie: J. Exper. Med. **48**:155, 1928.

Meanwhile, there is not the slightest evidence that the phagocytes or the fluids of the rabbit are able specifically to destroy a virulent human bacillus more easily than a virulent bovine one, or that the guinea-pig has a more efficient specific bactericidal defense against a strain of low virulence than against one of high virulence. Since whether progressive infection will or will not occur in any case depends entirely on whether or not the bacilli can proliferate freely in the body in question, the most that can be said is that the growth requirements of different types and strains of tubercle bacilli must be different, and that natural immunity may often depend entirely on whether or not a given animal body is able to satisfy those requirements. In the case of acquired resistance to the tubercle bacillus, the evidence at hand suggests, at least, that there has occurred in the resistant body some change which has placed it in a condition comparable to that responsible for natural immunity—a condition which merely renders the body a less favorable medium for parasitism by the tubercle bacillus. It is obviously of great importance to continue the attempt to determine what it is that inhibits parasitism in natural as well as in acquired immunity in all infections in which specific bactericidal properties of phagocytes or body fluids cannot be demonstrated.

I wish to emphasize that, in drawing into question the value of allergic hypersensitivity in acquired immunity, I am in no sense questioning the value and good service of the inflammation which attends the allergic reaction. This inflammation, however, appears to me to be directed primarily toward the neutralization of the noxious effects which tuberculoprotein exerts on the hypersensitive tissues, rather than to be an efficient bactericidal attack against the intact, living bacillus. It must be remembered that, in point of fact, the allergic reaction is not an evidence of greater resistance of the individual tissue cells to the protein of the bacillus, but of greater susceptibility. In the allergic, immune body, therefore, one is always confronted with what appears, at first sight, to be a paradox: the infected body is more susceptible at the same time that it is more resistant than the normal one. There is actually, however, no contradiction in this. The infected body prevents the growth and causes the death of the bacilli more readily than does the normal one—that is, it is resistant to living bacilli; at the same time, this resistant body is sensitized to the bacterial protein liberated into its tissues by the disintegration of the bacilli, just as it would become sensitized to any foreign protein introduced parenterally—that is, it is hypersusceptible to tuberculoprotein; for it is generally believed that it is not the intact, living tubercle bacillus which initiates the allergic reaction but, rather, the protein liberated by the disintegration of the bacilli. Even Zinsser, who holds the belief that allergic hypersensitivity is of fundamental importance in acquired immunity, because it sets the inflammatory mechanism

on a "hair-trigger," so to speak, has recently written the following: "Bacterial allergy is a condition in which the body is sensitized to a bacterial antigen. We believe that this antigen, in its most potent form, results from biological disintegration of the bacteria. . . . The allergic state represents an increased capacity on the part of the tissues to react to this antigen."[17] According to Zinsser's own definition, therefore, the allergic state in tuberculosis represents an increased capacity on the part of the tissues to react, not against living tubercle bacilli, but to an antigen which is liberated as a result of the disintegration of the bacilli. This means that when bacilli lodge in the tissues of the immune body, a mechanism responsible for their destruction must be in operation before the allergic inflammation appears.

I repeat that the capacity for developing hypersensitivity to protein must exist for some serviceable end; but it is one thing to believe that the reaction exists for some useful purpose, and quite another thing to believe that it protects the body against the tubercle bacillus. In spite of certain differences, the various forms of protein hypersensitivity are, in all probability, merely different manifestations of one fundamental type of reaction, which is brought into play under different conditions. What the basic intent of that fundamental reaction may be is not known. It has been suggested, for example, that it exists for the purpose of preserving the specificity of the protein of the species. However this may be, the disastrous effects of the repeated introduction of foreign protein into the blood stream (as exemplified by anaphylaxis), or into the tissues (as manifested by tuberculin allergy, or the Arthus phenomenon) may very well be accidental results of a highly organized, benign, serviceable mechanism which, under these circumstances, has been forced into action in situations and under conditions quite different from those which surround its intended activity. From such a point of view, a hypersensitive reaction initiated by the liberation of a bacterial protein from disintegrating bacilli has, basically, the same meaning as a hypersensitive reaction resulting from the deliberate forcing of egg-white into sensitized tissues. It is no more difficult for me to regard the allergic hypersusceptibility leading to tissue damage and inflammation in certain bacterial infections as an unfortunate accident, unnecessary for immunity and merely resulting from the parenteral liberation of foreign protein by the bacteria, than it is to regard the anaphylactic state as of no special use in immunity to bacteria; and, certainly, an animal may be highly anaphylactic to tuberculoprotein without possessing the slightest degree of acquired immunity to the tubercle bacillus; conversely, a superb degree of acquired immunity to the tubercle bacillus may be present in animals which are not anaphylactic at all. Those who feel, on general principles,

17. Zinsser: Bull. New York Acad. Med. **4**:351, 1928.

that since allergy appears during infection it must be of use in immunity, should remember that this other closely related hypersensitive state, anaphylaxis, may also be developed in tuberculosis although it is entirely unessential to immunity.

It is obvious that, if allergic hypersensitiveness is not necessary for immunity, procedures aimed at desensitization might be of great value, for desensitization would free the tissues from their disastrous tendency to necrosis, while leaving immunity intact. As a matter of fact, whatever beneficial effects attend tuberculin therapy can, to my mind, be best accounted for on the basis of the resulting depression of allergy, with the consequent greater opportunity for repair to proceed about foci of bacilli, unhampered by allergic destruction of the newly forming granulation tissue. It is interesting that Hamman and Wolman, in their book on tuberculin therapy,[18] make the following statement in their discussion of the patients who improve under repeated doses of tuberculin: "In the majority of cases," they write, "such a change for the better is associated with the development of a tolerance for tuberculin. This is a clinical fact, whatever our theories may be. . . . We must not blind ourselves to the well attested clinical observation that the average tuberculin patient shows, simultaneously with his improvement under tuberculin, a tolerance for tuberculin by whatever route. This remains a fact generally true, in spite of the citations of individual cases showing departures from this rule and in spite of oscillations of theories of immunity." I know that it is ordinarily assumed, not that depression of allergy has favored repair by removing an agency which tends to destroy connective tissue as rapidly as it is formed, but rather that the treatment stimulates the formation of connective tissue, and that allergy becomes depressed because the lesion becomes encapsulated. This I find difficult to believe, for aside from the fact that the method employed in successful tuberculin treatment is exactly the one best adapted for purposes of desensitization to foreign protein in general, it is difficult to believe that the encapsulation of a large tuberculous focus could so markedly reduce hypersensitiveness, while most normal adults carrying about small encapsulated foci retain it in a greater degree. Furthermore, allergy may by desensitization be reduced practically to zero in the human being and in the experimental animal in the presence of lesions which are progressive and by no means encapsulated.

If acquired resistance—the unknown mechanism which restrains the growth of the bacillus in the infected body—is actually (as I believe it probably is in tuberculosis) a thing separate from allergic hypersenstiveness and can be left intact after desensitization has restored the tissues to

18. Hamman and Wolman: Tuberculin in Diagnosis and Treatment, New York, D. Appleton & Co., 1912.

their normal indifference to tuberculoprotein, the security against necrosis which desensitization assures the tissues would certainly be of the greatest importance. Perhaps in some infections allergy does assist immunity by bringing bactericidal fluids and cells to the spot; but it is important, it seems to me, to do more than merely assume this as a generalization. It is important to study each infection with the purpose of determining, first, whether allergy is essential for immunity to the particular micro-organism under consideration; second, whether the allergic inflammation is actually an efficient bactericidal or growth-restraining agent as regards that particular micro-organism; third, to what degree the hypersensitivity acquired during that particular infection tends to kill tissue, for it is highly probable that this tendency will be found to be different in different infections; and, finally, from a weighing of the information acquired, to decide whether or not procedures aimed at desensitization should be attempted. In some infections the dissociation of allergy and immunity may be more easily effected than in tuberculosis. Dr. Chesney, Dr. Turner and I have recently obtained conclusive evidence of this in an experimental study of immunity and allergy in syphilis. Certainly, in tuberculosis, it is of great importance to know whether the local sacrifice of tissue (which itself, through allergic inflammation and allergic necrosis and softening is commonly enough a direct aid to the extension and spread of the bacilli) is actually necessary in any way for the protection of the body as a whole.

CONCLUSION

In conclusion let me say that I am keenly aware of the great attractiveness of the idea that bacterial allergy operates to destroy the invading microorganism, and perhaps it does not play an accessory rôle in certain infections, although I doubt that it is ever the essential basis of immunity. However, the enthusiastic eagerness with which this idea is so generally seized on in the case of tuberculosis may profitably be tempered by a critical examination of the evidence on which it rests. In this paper, I have been able to present only a few points in the analysis of that evidence, but I have wished to emphasize that in the present state of information in regard to tuberculosis it is wiser not to interchange too glibly the terms "allergy" and "resistance." Nor shall one profit by the use of such current evasive phrase as "allergy is an index of resistance," etc. The question to be met squarely is this: Is or is not tissue hypersensitivity to tuberculoprotein *necessary* for the more efficient destruction and restraint of growth of the tubercle bacillus observed in the body with acquired resistance? I have offered here a few of the numerous reasons for the belief that it may not be necessary, but further experimentation directed toward the solution of the problem is urgently required.

STUDIES IN FAT METABOLISM

II. THE CHARACTER OF BLOOD LIPIDS IN HEPATIC DISORDERS, INCLUDING MIGRAINE *

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The following article outlines results obtained from studies of the blood lipid of patients after the administration of single pure foodstuffs. It is a sequel of an earlier study [1] of normal persons. The investigation includes the quantitative determination of the lipid elements and, also, the iodine numbers of the cholesterol and total fatty acids of the whole blood of patients with organic or functional diseases of the liver.

The development by Bloor [2] of the well known micro-methods for the estimation of the lipids of the blood was followed by a number of independent investigations. The few that are of significance in the present investigation will be briefly reviewed. Those which are related only indirectly are discussed in the articles of Gibson and Howard,[3] Nicholls and Perlzweig,[4] Feigl [5] and Denis.[6] Comprehensive reports of the numerous investigations on the lipids of the blood in diabetes mellitus and in endocrine disturbances will be found in the articles of von Geelmuyden.[7] Denis [6] has correlated the literature on cholesterolemia, and has extensively reinvestigated the subject. From her observations she concluded that hypocholesterolemia occurred in acute infections, anemia and in cases of poor nutritional level. She further concluded that hypercholesterolemia existed only in severe diabetes, in pregnancy

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2. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **29**:437, 1927; A Method for the Determination of Fat in Small Amounts of Blood, ibid. **17**:377, 1914.

3. Gibson, R. B., and Howard, C. P.: Metabolic Studies in Pernicious Anemia, Arch. Int. Med. **32**:1 (July) 1923.

4. Nicholls, Elizabeth G., and Perlzweig, W. A.: The Plasma Fats and the Iodine Absorption Capacity of the Fatty Acids in Hyperthyroidism, J. Clin. Investigation **5**:195, 1928.

5. Feigl, Job: Ueber das Vorkommen und die Verteilung von Fetten und Lipoiden im menschlichen Blutplasma bei Ikterus und Cholämie, Biochem. Ztschr. **90**:1, 1918.

6. Denis, W.: Cholesterol in Human Blood Under Pathological Conditions, J. Biol. Chem. **29**:93, 1917.

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and in lipemia. Bloor [8] studied the lipid fractions in the blood of patients with a variety of clinical conditions. A comparison of the data was made with those obtained from normal subjects on the basis of magnitude and of the ratios of cholesterol to fatty acids and to lecithin. From these comparisons he concluded that disturbances in the fat metabolism were found in mitral stenosis, diabetes, carcinoma, malnutrition, chronic myocarditis, hypertension, nephritis, hemophilia, syphilis and chronic alcoholism. Gibson and Howard [3] found low amounts of whole blood and plasma fats in severe pernicious anemia. They also found that the amounts of the unsaturated fatty acids, as evidenced by the total iodine absorbed, were not excessive. Csonka [9] found unusually high percentages of the unsaturated fatty acids in a few pathologic conditions. Nicholls and Perlzweig [4] studied hyperthyroid disease. They found in untreated patients low fatty acids in the plasma associated with high iodine numbers. Feigl [5] examined the blood of jaundiced patients who had been fasting and who had such clinical conditions as cancer of the liver and gallbladder, acute and chronic cholecystitis, catarrhal jaundice and cirrhosis of the liver. Lecithin was increased above the normal values in cirrhosis but only in individual members of the other clinical groups. Both cholesterol and total fatty acids concentrations were frequently found increased in all clinical conditions enumerated.

During the present investigation observations were made on the blood of twenty-two patients. Three of these patients had cirrhosis of the liver, and two of them were deeply jaundiced. Autopsy was performed on only one of them. One patient, in whom a diagnosis of hemochromatosis was made, showed the characteristic pigment reaction in microscopic sections of the skin. Two patients with cancer of the liver were studied; autopsies were performed on both. Neither of these two patients was jaundiced. Six patients with uncomplicated toxic jaundice and six with uncomplicated migraine represented, obviously, clinical diagnoses. Four patients with gallstones were studied who showed neither jaundice nor other complications. Two of them came to laparotomy, in the other two the evidences of gallstones as shown by the x-ray pictures could not be questioned. All these patients were subjected to the usual clinical studies. In addition, roentgen examinations were made of the heart, lungs, gastro-intestinal tract and gallbladder after the use of sodium tetraiodophenolphthalein. Special studies were also made on the patients with migraine for possible evidences of cerebrospinal and endocrine disturbances. The patients studied were chosen because the symptomatology was so typical that the diagnosis in every case apparently could be accurately established.

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8. Bloor, W. R.: The Distribution of the Lipoids in Human Blood, J. Biol. Chem. **25**:577, 1916.

9. Csonka, Frank A.: The Fatty Acids in Human Blood in Normal and Pathological Conditions, J. Biol. Chem. **33**:401, 1918.

METHODS AND PROCEDURES

All observations were started fifteen hours after the ingestion of any food. The studies comprised series of observations beginning with the fasting state and continuing after the administration of oleic acid, olive oil, hard boiled egg white or chemically pure dextrose. During all observations the patients were reclining and were allowed water to drink in any quantity desired. The methods of administration were: (*a*) 25 cc. of oleic acid mixed with 75 cc. of tap water and administered intraduodenally; (*b*) 50 cc. of olive oil was given by mouth, followed by 200 cc. of tap water; (*c*) 240 Gm. of finely divided hard boiled egg white was eaten, supplemented with 200 cc. of tap water, and (*d*) 100 Gm. of dextrose dissolved in 200 cc. of water was ingested orally. A specimen of blood was taken as a control from the median basilic vein just before the administration of food. Thereafter the operation was repeated at approximately hourly or bihourly intervals for seven hours. Each specimen of blood represented a volume of 20 cc. to which about 40 mg. of lithium oxalate was added to prevent clotting. The following determinations were made: lecithin-phosphorus, cholesterol, total fatty acids and the iodine numbers of the latter two substances. The iodine number was determined by the method devised by us and described in a previous article.[1] In the same article there was described a slight modification for saponifying the cholesterol esters by the method of Bloor, Pelkan and Allen[10] for cholesterol and total fatty acids in the blood. This modification was employed in the present investigation.

OBSERVATIONS

During the Fasting State.—The results of the measurements made on the blood of fasting patients may be compared with those previously found in normal blood by studying the accompanying table. Such an examination shows the following deviations from the normal measurements:

The Lecithin-Phosphorus, Cholesterol, Total Fatty Acids and the Iodine Numbers of the Latter Two of the Blood of Fasting Patients and Normal Subjects

Diagnosis	Number of Subjects	No. of Determinations	Cholesterol, Mg. per 100 Cc.	Cholesterol Iodine Number	Fatty Acids, Mg. per 100 Cc.	Fatty Acid Iodine Number	Lecithin-Phosphorus, Mg. per 100 Cc.
Normal	14	59	199- 99	.....	461-295	83.4-18.4	
	5	15	.....	240-108			
	6	39	.....	.....	.....	.....	18.6- 9.4*
	8	20	.....	.....	.....	.....	22.4-10.9†
Migraine	6	13	200-129	.....	450-251	119-45.3	
	4	10	.....	152.3-42.5	.....	.....	12.4- 8.7*
	2	3	.....	.....	.....	.....	17.7-13.2†
Gallstones	4	9	217-143	.....	420-229	90.4-25.2	
	2	6	.....	101-53.2	.....	.....	12.2-10.6*
	2	3	.....	.....	.....	.....	15.8-13.0†
Cirrhosis of the liver	3	9	370-135	142-50.7	829-256	81.1-50.8	18.8- 8.9*
Jaundice	6	14	430-130	102-38.2	870-292	93.5-15.0	
	5	13	.....	.....	.....	.....	47.1-10.6*
	1	1	.....	.....	.....	.....	18.1†
Hemochromatosis	1	2	235-203	108-96	502-440	75.3-56.1	13.9-12.7*
Cancer of liver	2	2	214-187	117	577-468	47.0-47.0	11.6*

* Method of Fiske.
† Method of Hess.

10. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, J. Biol. Chem. **52**: 191, 1922.

1. Except in patients with migraine, cholesterol concentration was definitely increased above the normal amount in some members of all groups.

2. The iodine number of cholesterol showed a marked decrease in certain members of all groups except in patients with cancer of the liver, in whom only one determination was made.

3. Total fatty acids were increased in certain members of all groups except in patients with migraine and gallstones.

4. Unusually high iodine numbers of total fatty acids were present in patients with migraine, gallstones and cirrhosis.

5. Lecithin-phosphorus was increased in two patients. One of these had diabetes with toxic jaundice, and the other, cancer of the liver without jaundice.

These observations show that in all groups of fasting patients some of the various determinations differed markedly from those obtained on normal fasting subjects.

Following the Ingestion of Foodstuffs.—An essential purpose of the present investigation was to obtain data on the blood lipids of patients which could be compared with the observations in normal subjects. The character of data found permits comparative studies to be made of differences in amounts and, also, of the times at which these differences occurred. Variations in the magnitude of differences in quantity can be most easily demonstrated by plotting the results in percentages. For this reason, on the charts used throughout the text, they have been plotted so as to show plus or minus the percentage of variation from the fasting levels; taken as 100, the values for the "fasting" blood lipids are appended to each chart. This permits the calculation of the actual amounts found during any given period of observation.

Cholesterol Concentration.—The cholesterol concentration of the blood was studied following the ingestion of the various foodstuffs by the different groups of patients. The average values of the hourly variation of the groups, under the stimulus of the several test meals, have been plotted in percentages in chart 1. For purposes of comparison, curves of the values found in normal subjects are included. Two curves are plotted for the normal variation in cholesterol after ingestion of fat. One of these curves shows the effects of the ingestion of olive oil. The second represents the average of two curves, one of which plots the effect of the ingestion of olive oil and the other the effect of the administration of oleic acid. This second curve forms the basis for comparison with the results in those groups in which the patients received both olive oil and oleic acid meals.

Chart 1 shows that variations in cholesterol from the fasting level were not great. Only three curves, however, approximated that for

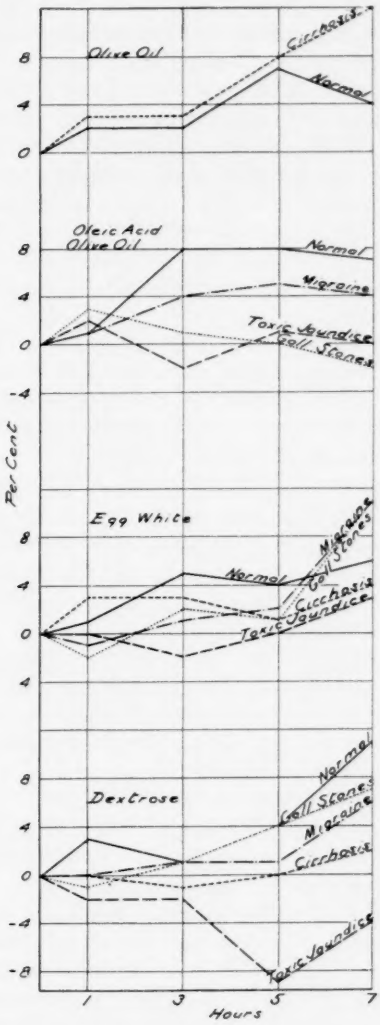

Chart 1.—The percentage of variation from the fasting level of cholesterol concentration after the ingestion of food. The actual values per hundred cubic centimeters of fasting blood preceding the three types of meals were: olive oil, cirrhosis 208 mg.; olive oil or oleic acid, migraine 168 mg.; toxic jaundice, 203 mg. and gallstones 179 mg.; egg white, migraine 155 mg., gallstones 157 mg., cirrhosis 216 mg., toxic jaundice 248 mg.; dextrose, gallstones 165 mg., migraine 180 mg., cirrhosis 237 mg. and toxic jaundice 174 mg.

the fasting level. These three curves represent the cholesterol concentration in patients with gallstones and jaundice after the ingestion of fat and in those with cirrhosis following the administration of dextrose. The other curves show greater variations above or below the fasting levels. The cholesterol concentration of the patient with hemochromatosis, not charted, was but slightly affected by either the fat or the protein meals. On the other hand, following the ingestion of fat by two patients with cancer of the liver, the cholesterol concentration, not charted, showed an average increase of 10 per cent above the fasting level. These observations show that the test meals exerted influence on the cholesterol concentration of the blood in the great majority of the patients studied.

The only curve found to be consistently increased above the normal is that following the ingestion of fat (olive oil) by the patients with cirrhosis. With minor exceptions, all other curves show that the various types of foodstuffs influenced cholesterol concentration of the blood of patients less than that in normal controls.

Iodine Number of Cholesterol.—Following the ingestion of food, variations in the iodine numbers of the cholesterol in patients with migraine, gallstones and toxic jaundice were sufficiently uniform to permit the construction of average curves for each group. These curves, which represent the percentage of variation from the fasting level, are plotted in chart 2.

With minor exceptions, the curves for the iodine numbers of the cholesterol of the patients with jaundice and gallstones showed a great increase above the fasting levels after the ingestion of all foodstuffs. A comparable increase was found in the patients with migraine after the ingestion of protein, while after the ingestion of fat and dextrose the curves were increased above the fasting levels only during the latter part of the period of observation. These increases form curves running in the opposite direction to those of normal subjects.

A group of three patients with cirrhosis of the liver was studied. Two of the patients were deeply icteric, while the third showed no jaundice. Decrease in the iodine numbers of the cholesterol occurred after all types of meals in one icteric patient, but only after the ingestion of dextrose in the other. Comparable decreases followed the ingestion of fat and protein by the nonjaundiced patient. The iodine numbers of cholesterol were increased after the ingestion of fat and protein by one icteric patient and after dextrose by the nonjaundiced patient. These observations in the patients with cirrhosis divide themselves into two types. One type is characterized by a decrease in the iodine number of cholesterol and is comparable to the observations in normal subjects. The other type is characterized by increases in the iodine numbers of cholesterol, and in this way differs from the normal observation.

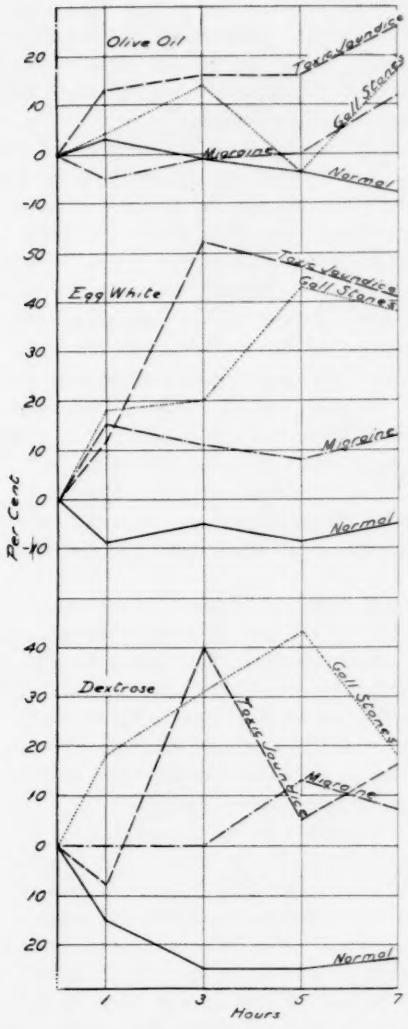

Chart 2.—The percentage of variation from the fasting level of the iodine numbers of cholesterol after the ingestion of food. The actual iodine numbers of fasting blood preceding the three types of meals were: olive oil, toxic jaundice 84.1, gallstones 91.6 and migraine 93.6; egg white, toxic jaundice 65.9, gallstones 77 and migraine 100; dextrose, gallstones 77.1, toxic jaundice 66 and migraine 92.6.

The iodine numbers of cholesterol were moderately increased after the ingestion of fat in the blood of one patient with cancer of the liver. The cancer was secondary to carcinoma of the gallbladder, and the patient was not jaundiced. In the patient with hemochromatosis the iodine numbers were much increased following the protein meal, while ingestion of fat had but little influence.

The observations discussed show that decreases in the iodine numbers of cholesterol followed the ingestion of food in a small number of cases, while in the great majority the numbers were increased. Such increases form curves that are strikingly different from the uniformly depressed curves which followed ingestion of food by normal subjects. These changes in the iodine numbers show that ingested foodstuffs influenced the chemical character of the fraction of the blood extract containing cholesterol or its esters.

Total Fatty Acids.—Average curves for the variations in the percentage of total fatty acids, which followed the ingestion of food, could be plotted as follows: (*a*) for patients with migraine and cirrhosis after all types of meals; (*b*) for those with toxic jaundice after foodstuffs composed of proteins and carbohydrates; (*c*) for four patients with toxic jaundice after the fat meal, and (*d*) for those with gallstones following the ingestion of fat. The curves are given in chart 3.

All curves in chart 3 showed increases in the concentration of total fatty acids above that of the fasting level. The persistence of these increases, however, was interrupted in the patients with jaundice after the ingestion of both protein and dextrose. The interruption was due to decreases below the fasting level during the first half of the observation periods. After the ingestion of dextrose, the magnitude of the decrease equalled that of the maximum increase, while after the ingestion of protein, the decreases were slight. The two patients with toxic jaundice, the data for whom were not included in the graph of chart 3, showed unusual reactions to the fat meal. The concentration of total fatty acid of the blood in both these subjects increased markedly during the first half of the observation periods and then dropped abruptly to below the fasting level. The decrease below the fasting level was moderate in one subject, while in the other it diminished the concentration of fatty acid to but 50 per cent of that level. Well marked increases in the concentration of total fatty acids of the blood were found in one patient with cancer of the liver, after the ingestion of fat. Comparable increases were found after ingestion of protein by a patient with hemochromatosis, and by two patients with gallstones. Such increases were also found after the ingestion of dextrose by the patient with hemochromatosis, and by one of the patients with gallstones. Following the ingestion of dextrose one patient with gallstones showed

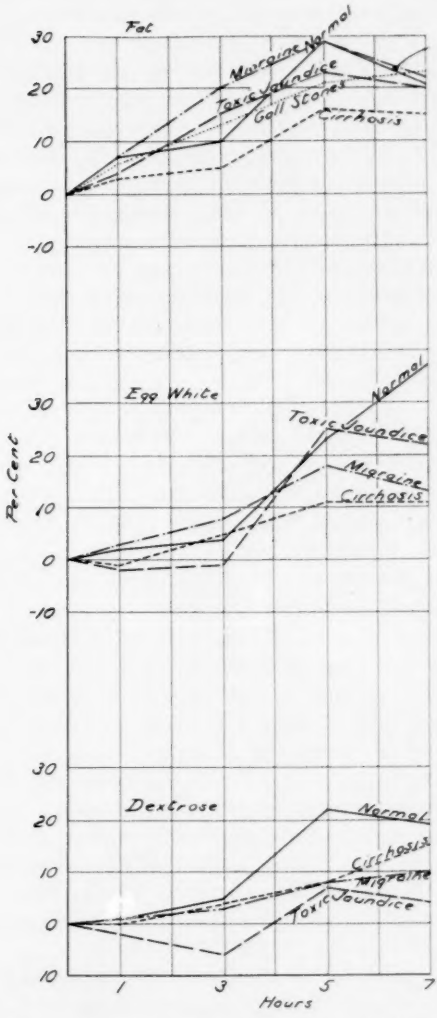

Chart 3.—The percentage of variation from the fasting level of the concentrations of total fatty acid after the ingestion of food. The actual values per hundred cubic centimeters of fasting blood preceding the three types of meals were: olive oil, migraine 326 mg., gallstones 370 mg., toxic jaundice 385 mg. and cirrhosis 517 mg.; egg white, toxic jaundice 523 mg., migraine 357 mg. and cirrhosis 454 mg.; dextrose, cirrhosis 412 mg., migraine 326 mg. and toxic jaundice 440 mg.

a persistent, moderate decrease of the concentration of fatty acid in the blood below that of the fasting level. A comparable decrease of much greater magnitude was found in one patient with cancer of the liver after ingestion of fat. This patient was not jaundiced. The foregoing data demonstrate that the ingestion of food influenced the concentration of the total fatty acids of the blood in all types of patients studied.

The influences of ingested foodstuffs on the blood lipids of patients may be compared with those found in normal subjects from data given in chart 3 and the description of results discussed in the text. Except for a few minor observations and one of the curves for the group with migraine, the curves plotted in chart 3 for patients were of less magnitude than those representing the observations in normal subjects. The character of the decrease in the concentration of the total fatty acids below the fasting level, which was described for certain patients with cancer, gallstones and toxic jaundice, is entirely different from any found in normal subjects. Following ingestion of protein, increases failed to be maintained in the concentration of the total fatty acids in the three groups of patients for whom the results are plotted on chart 3, and in one patient with gallstones. This phenomenon caused the shape of the curve to differ sharply from that representing the normal condition. Except for the one patient with hemochromatosis, therefore, certain observations in all types of patients studied showed well marked differences from those of normal subjects.

Iodine Numbers of Total Fatty Acids.—Curves representing the variations in the percentage of iodine numbers from the fasting levels were of comparable character in the majority of the members of each group of patients. For descriptive purposes the components of comparable curves can be plotted and presented as a single curve. Such average curves have been plotted for four patients each of the groups with migraine, toxic jaundice and gallstones, following ingestion of the fat meal. After ingestion of protein, curves were plotted for four members of the group with toxic jaundice and for three members each of the groups with migraine and cirrhosis. Curves for the latter two groups were plotted, also after the ingestion of dextrose. The curves are given in chart 4.

Excepting the latter half of the observation period after the protein meal, the three curves for the iodine numbers of the cirrhosis group are all well above the fasting level. After the fat meal the curve for the jaundice group approximated that of the fasting level. The other six curves are well below the fasting level.

Members of the various groups of patients who gave curves for the iodine numbers differing widely from the majority are not represented on chart 4. Such curves were found after the ingestion of fat by two patients with migraine. One of these curves was persistently well above

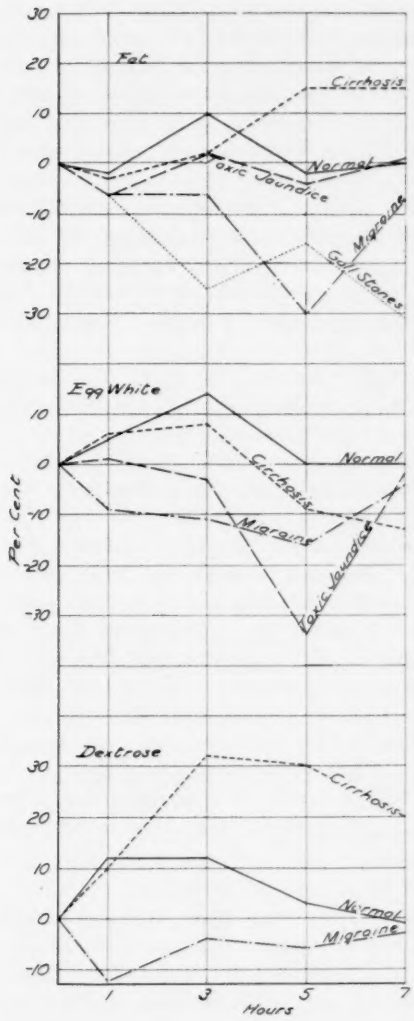

Chart 4.—The percentage of variation from the fasting level of the iodine numbers of total fatty acid after the ingestion of food. The actual iodine numbers of fasting blood preceding the three types of meals were: olive oil, cirrhosis 63.4, toxic jaundice 76.5, migraine 82.2 and gallstones 57; egg white, toxic jaundice 77.5, migraine 85.3 and cirrhosis 59.7; dextrose, cirrhosis 53.5 and migraine 86.4.

the fasting level. The other curve showed an abrupt increase to 60 per cent above the fasting level and then during the last half of the observation period dropped to 20 per cent less than the fasting level. Comparable increases were found after the protein meal in two patients with jaundice, after the ingestion of dextrose by another, and after the fat meal in a patient with cancer of the liver. On the other hand, after ingestion of dextrose by two patients with jaundice the curves for the iodine numbers were persistently moderately depressed below the fasting level. Two patients with gallstones received the protein and dextrose meals; the fat meal was given to a second patient with cancer of the liver, and a patient with hemochromatosis ingested the fat and protein meals. The curves for the iodine numbers in these patients were indiscriminately moderately increased above or decreased below the fasting level.

The foregoing data show that the ingestion of food influenced the character of the circulating lipids as evidenced by changes in the iodine numbers of the total fatty acids.

The curves for the iodine numbers plotted on chart 4 are representative of the observations in all patients studied. For this reason comparison of these curves with those for normal subjects affords a readily comprehended demonstration of the relative differences of the influence of the ingestion of food on the blood's lipids, as shown by the changes in the iodine numbers. The chart shows that the curves for patients were either increased above that of the normal or decreased below it. Excepting one curve of the jaundice group, such deviations from the normal curves were well marked. Further, the curves for certain patients were of an entirely different shape from that of normal subjects; as for example, the curve of the gallstone group after the ingestion of fat. From these observations it is concluded that the character of the changes in the iodine numbers shows that the ingestion of food influenced the lipids of the blood of patients differently from those of normal subjects.

COMMENT

Concentrations of the various lipids of blood from fasting normal subjects were studied by Bloor.[8] The limits of variation for the total fatty acids and lecithin reported by him are fully comparable to those in the present investigation. He made an analysis of the blood of twenty-three subjects and found the limits of variation in cholesterol to lie between 190 and 250 mg. per hundred cubic centimeters of blood. The authors made fifty-nine determinations on fourteen normal subjects and found the variations between 99 and 199 mg. However, the methods for determining the cholesterol concentration used in the two investigations differed somewhat. The method employed by Bloor [2] was one in which the extract analyzed contained fatty acids and possibly

other alcohol soluble substances. In the newer method of Bloor,[10] used in the present investigation, the extract is so treated as to be free from these alcohol soluble substances. This difference in methods may explain the lower values obtained by the authors. For this reason the limits found during the present investigation will be accepted as the basis for comparison with the observations on the blood of fasting patients. On this basis, cholesterol concentration was much increased above the normal in a patient with cirrhosis of the liver. This patient was deeply jaundiced, but did not have diabetes. Comparable increases were found in two patients with diabetes mellitus. One of these patients represented diabetes mellitus complicated with toxic jaundice, and the other hemochromatosis. Slight hypercholesterolemia was found in one patient with gallstones and one with uncomplicated toxic jaundice. Excluding diabetes, therefore, definite hypercholesterolemia was found in only the patient with cirrhosis of the liver. The infrequency of hypercholesterolemia in the types of clinical conditions studied confirms the observations of Denis,[6] previously discussed.

Excepting a single determination in one patient with cancer of the liver, low iodine numbers for cholesterol were found in all groups of fasting patients. These iodine numbers are so low that they form striking contrasts to those found in normal subjects. In a few fasting patients the total fatty acids were much increased above the normal amount. Diabetes mellitus may explain the increase in two of them, but it was also found in the absence of diabetes, in one nonjaundiced patient with cancer of the liver, in one icteric patient with cirrhosis, and in one with toxic jaundice. Feigl[5] also found hyperlipemia in jaundiced patients. The iodine numbers of the total fatty acids of the blood were considerably increased above the normal in certain fasting members of the groups of patients with migraine, gallstone, cirrhosis and toxic jaundice. The abnormal iodine numbers for cholesterol and total fatty acids and the hyperlipemia found are indications of disturbances in the lipid metabolism. The involvement of the liver in all the patients suggests that it played a rôle in producing these disturbances.

The lecithin-phosphorus was decidedly increased above the fasting normal level only in the presence of diabetes, in which condition it is a common observation.

Increases in total fatty acids frequently followed the ingestion of all types of meals. When such increases followed the ingestion of fat, the iodine numbers showed that the fatty acids were of a different chemical constitution from those present in the fat of the food ingested. These phenomena are comparable to those found in normal subjects under similar experimental conditions, and previously reported.[1] For this reason, they permit the same interpretation of their significance, which is that the fatty acids absorbed during digestion did not accumu-

late in demonstrable amounts in the blood stream. Therefore, changes in the character or concentration of the blood's lipids were most probably the result of their mobilization from the tissues of the body. The same conclusion was drawn from comparable phenomena observed in the study of normal subjects.[1]

The influence of ingested foodstuffs on the lipids of the blood of patients has been compared with arbitrary normal standards. Such standards were established previously by extensive observations on normal subjects.[1] The curves by which this comparison was made demonstrated well marked differences both in magnitude and in shape between the results in patients and those in normal subjects. No particular type of change was confined to any one kind of meal. The most striking differences occurred in the iodine numbers of cholesterol. These were persistently much increased in patients, while they were uniformly decreased in normal subjects after the ingestion of all types of foods. The iodine numbers of the total fatty acids, also, differed from those found in normal subjects under similar experimental conditions. Following the test meals the concentrations of total fatty acids and of cholesterol were usually increased less in the blood of patients than in that of normal subjects; but occasionally great increases above the normal did occur. All these variations from the normal are interpreted as the result either of the presence in the blood of abnormal forms of lipids or of merely abnormal reactions to stimulation of the tissues from which the lipids were liberated. Either abnormality apparently can be ascribed only to disturbances in metabolism. Thus, disturbances in lipid metabolism have been demonstrated in the presence of organic lesions of the liver characterizing cancer, cirrhosis and toxic jaundice; also in chronic cholecystitis with stones, and in uncomplicated migraine. All the patients affected with cholecystitis and with migraine showed well defined hepatic dysfunction, as demonstrated by the analysis of duodenal bile. The occurrence of hepatic dysfunction cannot be questioned in the presence of the organic lesions of the liver enumerated. Nevertheless, its presence was confirmed by the observation of an abnormal condition in the duodenal bile, by increases in the icteric index and by the van den Bergh reactions in the blood serum. Therefore, the observed abnormalities in the lipid metabolism were associated with demonstrated disturbances in the functional state of the liver. At the time the experimental observations were conducted the general physical conditions of all patients, except one with cirrhosis, were not seriously impaired. For this reason, secondary effects of the various pathologic conditions on the patients were evidently not the primary cause for the disturbances found in either the lipid metabolism or the functional state of the liver. The coincidence of the latter two disturbances suggests either that the hepatic dysfunction played a rôle in

the production of the abnormal lipid metabolism or that both disturbances were due to a common cause.

The presence in the blood of lipids with unusual iodine numbers does not necessarily signify the formation of abnormal chemical combinations. Such iodine numbers may be explained by assuming an augmented formation of types of lipids normally present. Since Leathes [11] contends that changes in the degrees of unsaturation of fatty acids are a function of the liver, such augmented formation could result from disturbance in this function. The observations, however, merely suggest but do not prove such a phenomenon.

The chemical significance of variations in the iodine numbers of cholesterol was discussed in a former communication.[1] It was suggested that tautomeric forms could account for the variations found. It was emphasized, however, that because of the possible substituting action of iodine [12] further studies would be necessary before a definite interpretation could be made. During the course of the present investigation the iodine numbers demonstrate that in the blood of the patients studied the fraction containing cholesterol was of widely different chemical nature from that found in the blood of normal subjects under similar experimental conditions. Such observations, obviously, furnish further evidence of the existence of mixtures of different forms of cholesterol in the blood. This possibility is supported by the observations of Anderson.[13] A more detailed discussion of the chemical, biochemical and pathologic significance of the data will be left to a future communication.

The concentration of lecithin, as shown by the quantitative determination of lecithin-phosphorus, was uninfluenced by the ingestion of the various test meals. These observations are comparable to those in normal subjects.

SUMMARY AND CONCLUSIONS

A study of the fat metabolism, as reflected in the lipids present in the blood stream, was made on patients with cirrhosis of the liver, cancer of the liver, chronic cholecystitis with biliary calculi, toxic jaundice, hemochromatosis and migraine. In all these patients functional disturbances of the liver were demonstrated.

1. Hyperlipemia, abnormally low iodine numbers for cholesterol and unusually high ones for fatty acids of the blood during the fasting state

11. Leathes, J. B., and Raper, H. S.: The Fats, New York, Longmans, Green & Company, 1925.

12. MacLean, I. S., and Thomas, E. M.: On Abnormal Iodine Values, with Special Reference to Sterols and Resins, Biochem. J. **15**:319, 1921.

13. Anderson, R. J.: Properties of Cholesterol Obtained from Different Sources, J. Biol. Chem. **71**:407, 1926-1927.

are indications of disturbances in lipid metabolism in patients with the diseases studied.

2. As shown by changes in the iodine numbers and in the concentrations, ingested foodstuffs influenced the character of the lipids of the blood of patients studied. The influence on the character of the lipids was usually comparable after all types of test meals, and in all conditions studied. Qualitative and quantiative differences, however, were frequent and occasionally strikingly great.

3. When presented graphically, the observations in patients determined curves differing in magnitude and in shape from those obtained with normal subjects. The occurrence of such differences is interpreted as the result of abnormal metabolism.

4. The gross changes in the lipids of the blood of patients, demonstrated after the ingestion of food, are interpreted as the result of their mobilization from the tissues of the body. The character of the iodine numbers of the lipids so mobilized suggests that they either were of abnormal form or represented an abnormal reaction of the tissues to stimulation.

5. The observations suggest that the cholesterol of the blood of the patients studied differs in chemical constitution from that of normal subjects.

6. The occurrence of abnormal lipid metabolism in the presence of hepatic disturbance indicates either that the liver played a rôle in its production or that both abnormalities were due to a common cause.

7. The lecithin-phosphorus concentration of the blood was not demonstrably influenced by the ingestion of food.

Book Reviews

A History of Pathology. By Esmond R. Long, Ph.D., M.D., Professor of Pathology, University of Chicago. Price, $5. Baltimore: Williams & Wilkins Company, 1928.

Dr. Long has presented an excellent history of pathology — a book long overdue in the English language — and a book that offers convincing evidence of the desirability of having men who are active in the specialty write the history of special medical fields, provided, of course, that their literary ability and historical discrimination approach that of Dr. Long.

Dr. Long was faced with the difficulty of taking the reader through the muddled and chaotic thoughts from Hippocrates, through Celsus and Galen and the days of the Renaissance, to the time when Morgagni correlated the "Seats and Causes of Disease" with clinical symptoms. But Dr. Long has accomplished this tedious business in admirable fashion. It is most difficult for the modern man, born into a cellular age, to reconstruct the ideas and intellectual environment of those days. The ancients still await their true interpreter to us.

But from Morgagni on, Dr. Long became truly eloquent, restrained only by his scientific training and academic background. One can see the seed of pathology sprout and grow; Hunter becomes a living being instead of a name; Bichat thinks; Muller is slighted but forces himself onto the page; Rokitansky, the indefatigable, speaks, not only from his picture but also from the printed page, and Virchow, whom one has awaited from the frontispiece, asserts his hard, rugged master mind. The mistakes these men made, particularly Rokitansky and Virchow, are emphasized and in such a fashion as to make the reader, who is conscious of his daily errors, feel less humiliated. It is good reading for the man with an inferiority complex.

Then the great Koch stalks on the scene — the man who made the science of bacteriology almost single handed. This advent of etiology in the field of objective pathology is a thrilling chapter, better than a novel. What a pity that the pages limit the description of these times; if only the author might have added something more of the characters and private lives of these two giants, Virchow and Koch, illuminated by the sparks generated when flint struck on steel.

Cellular pathology, etiology and immunology, all developing with feverish activity, all in one generation, inspire the reader with the hope of the conquest of all infectious diseases, as it did the men of those days, in spite of the fact that the reader knows beforehand the disappointing sequel. The bitter battle of inflammation, fought on the field of a frog's cornea, is real; one still hears reverberations of the conflict.

The book has been written for students and pathologists but should interest all physicians, even surgeons. It may not add pennies to his purse for a physician, who has made a diagnosis of Addison's disease or arteriosclerotic kidney or aortic insufficiency or tuberculosis, to know who first saw these things clearly with a pathologic understanding, and when and how, but it would add a mite to his pleasures in life. He can find that pleasure in Dr. Long's book.

One dark thread runs through the woof and warp of the history, the story of neoplastic diseases. Hippocrates knew them, and they are now known; it is known that they are cellular. Present observers study them objectively, as Rokitansky observed typhoid ulcers, and grope about with theories possibly as unfounded as were Rokitansky's notions of the typhoid crasis. Long sees the immediate future of pathology in chemical and experimental pathology. May these brain children of Virchow's solve the "Riddle of the Neoplasm."

MONOGRAPHIEN AUS DEM GESAMTGEBIET DER PHYSIOLOGIE DER PFLANZEN UND DER TIERE. By M. GILDEMEISTER, Leipzig; R. GOLDSCHMIDT, Berlin; C. NEUBERG, Berlin; J. PARNAS, Lemberg; W. RUHLAND, Leipzig. Fünfzehnter Band: Die Aeussere Sekretion der Verdauungsdrüsen. Von B. P. Babkin, Dr. med. (St. Petersburg), D.Sc. (London), Professor der Physiologie an der Dalhousie Universität, Halifax N.S. (Canada). Second Edition. Price, 68 marks. Pp. 860, with 145 illustrations. Berlin: Julius Springer, 1928.

It is impossible to summarize this large work on the external secretions of the digestive glands. The first edition appeared in 1914, and hence, after nearly fifteen years, a complete revision was necessary. The general plan of the earlier text is followed in the present one, but the additions and amplifications are numerous and extensive. The number of illustrations is increased from 29 to 145. Several new chapters are included, among them being The Continuous Gastric Secretion, The Blood Supply of the Pancreas, The Secretion of Bile and The Function of the Gall Bladder. Considerable attention is paid to the author's own work and to that of his co-workers in Odessa and in Halifax, but the majority of the book consists in a thorough discussion and citation of the literature which has been reviewed carefully through 1926. It constitutes a valuable reference book for all those interested in any way in the digestive glands.

RÉNÉ THÉOPHILE HYACINTHE LAENEC: A MEMOIR. By GERALD B. WEBB, Price, $2. New York: Paul D. Hoeber, 1928.

This small volume has all the lure of romance, and at the same time, gives one the feeling of exhilaration which comes from an intimate appreciation of one of the earth's great spirits. For not only was Laenec a brilliant investigator, but he had a most richly and diversely endowed personality. It is evident from the sympathy and insight with which the subject is treated that the author has a great admiration and appreciation for him. He depicts most strikingly how in spite of poor health, poverty and a brief span of years Laenec accomplished one of the monumental advances in the knowledge and control of human disease. The historical setting and contemporary personages, both medical and nonmedical, are well portrayed.

This book should be read by every medical student; it will afford several delightful hours to those interested in the development of the knowledge of disease in man, tuberculosis in particular.

PRAKTISCHE DIFFERENTIALDIAGNOSTIK. BAND I, TEIL 4, ERKRANKUNGEN DER VERDAUUNGSORGANE. By PROF. DR. LOUISE R. GROTE. Price, 6.80 R. M. Dresden and Leipzig: Theodor Steinkopff, 1928.

This new part of the collection of independent articles on practical differential diagnosis proves to be of special interest for the general practitioner and student. Written by a man who is the leading physician of one of the oldest and best known sanatoriums in Germany, this book reflects the vast experience of one who knows how to examine patients by means available to every physician. Observation of the patients and the evaluation of their subjective symptoms and all important signs of gastro-intestinal disturbances are the outstanding features of the clinical attitude of the author. In a most interesting fashion, he discusses coated tongue, localized abdominal pains, etc., as well as the questions concerned with the constitutional factors of the patient. The book is highly recommended to the physician and student.

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